TEXAS
The University of Texas at Austin

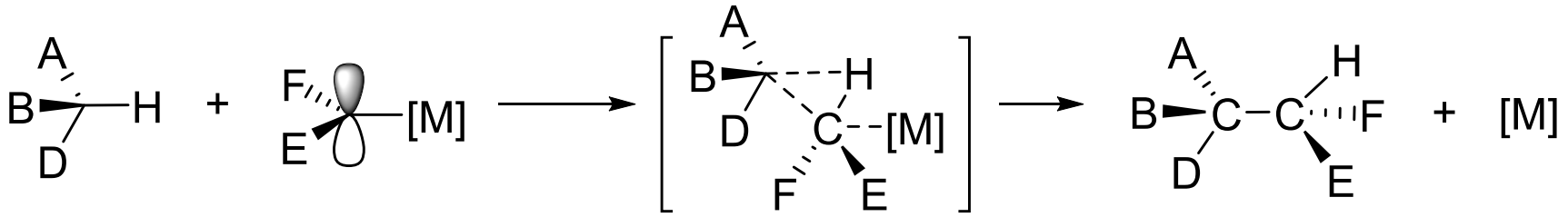
Guangbin Dong Group Meeting @ UT Austin

Metal Carbene-Involved C-H Functionalization --New Pathways and Synthetic Applications

Dong XING
March 9th 2016

Metal Carbene-Involved C-H Functionalization

Sp3 C-H Functionalization



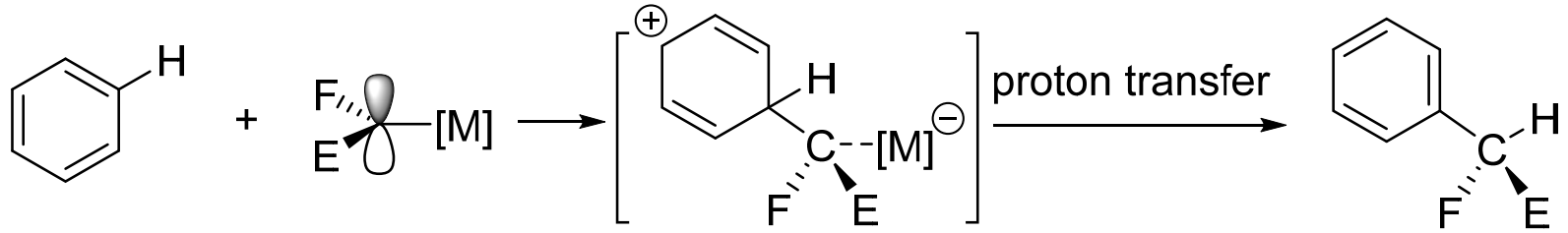
The C-H activation/C-C formation proceeds in a single step through a three-centered hydride transfer-like transition state with a small activation energy

This concerted three-centered transition state allows efficient asymmetric control by chiral metal catalysts

Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181

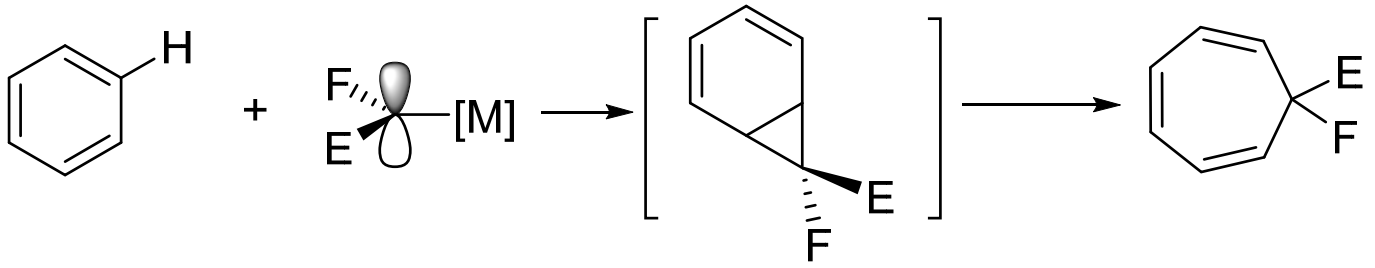
Metal Carbene-Involved C-H Functionalization

Aromatic sp2 C-H Functionalization



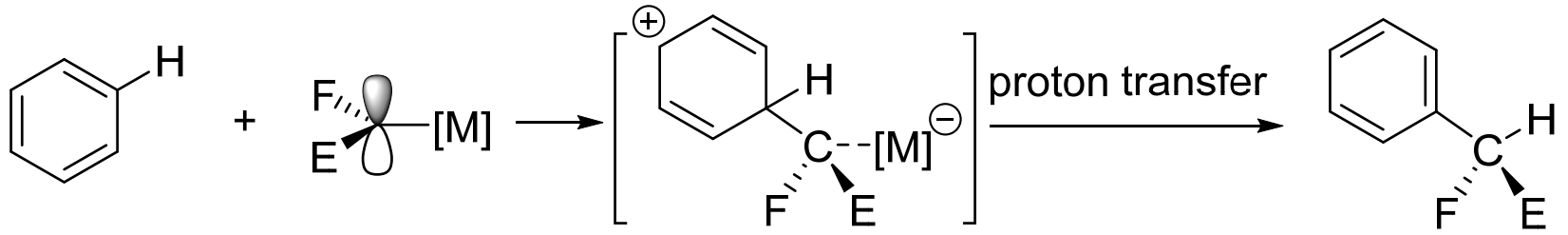
zwitterionic intermediate

Competitive Buchner Ring Expansion

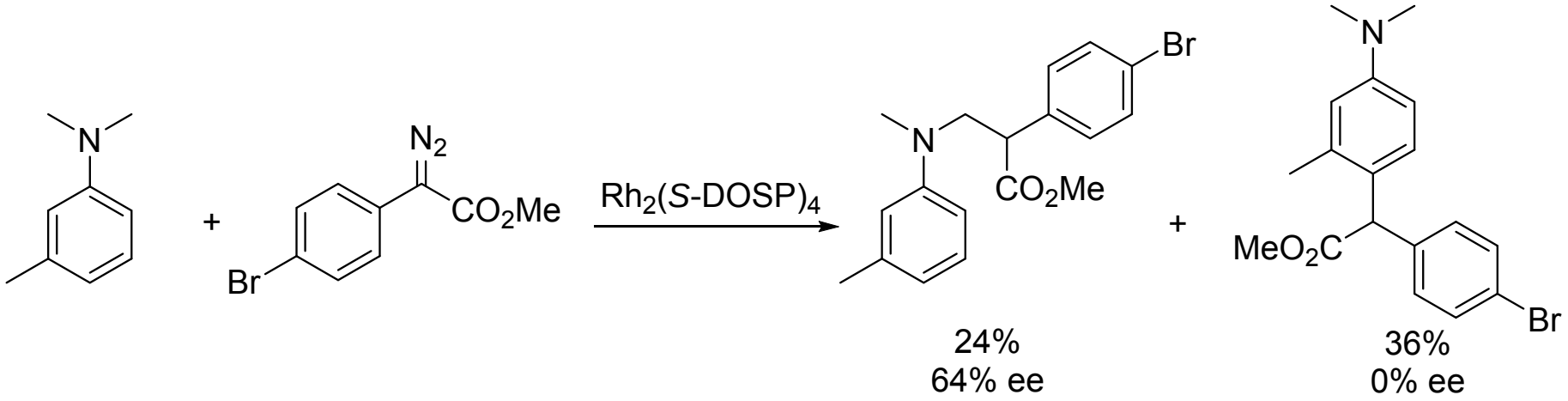


Metal Carbene-Involved C-H Functionalization

Aromatic sp2 C-H Functionalization

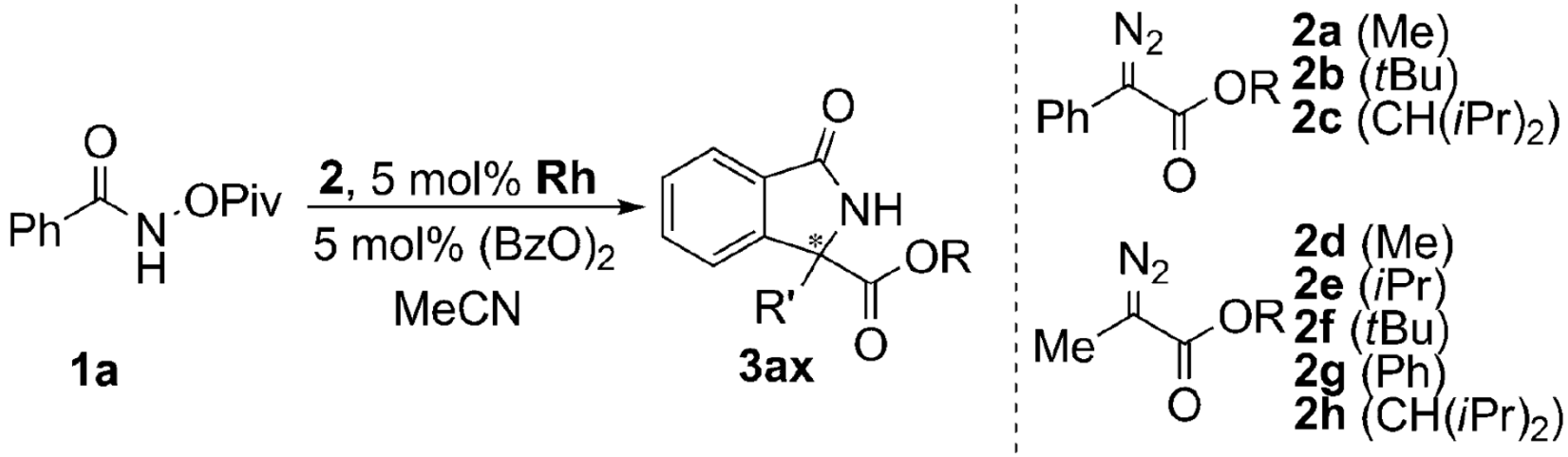


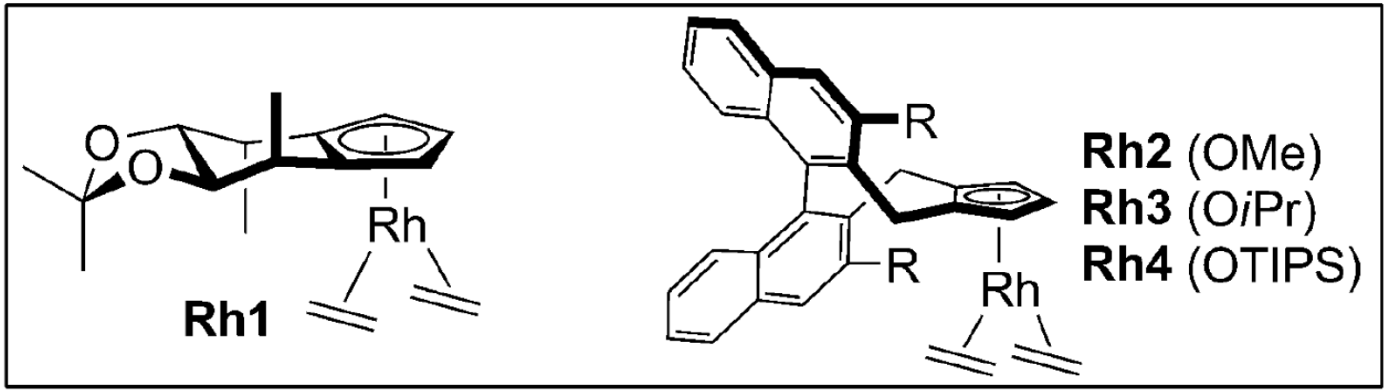
The zwitterionic intermediate-involving pathway makes it difficult to achieve asymmetric control by chiral metal catalysts



Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004**, *6*, 1769

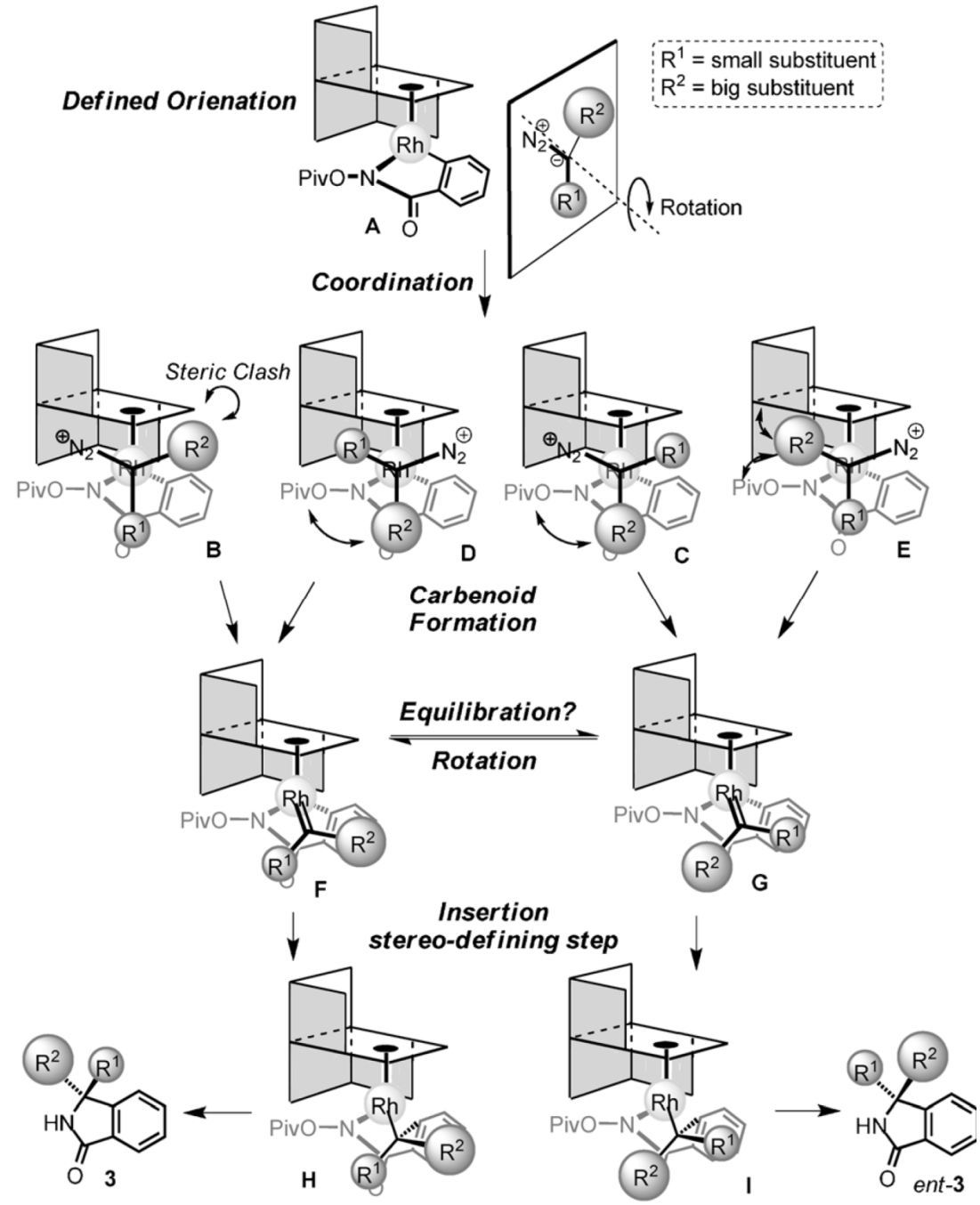
Directing Group-Assisted Enantioselective Aromatic C-H Functionalization via "CMD" Mechanism



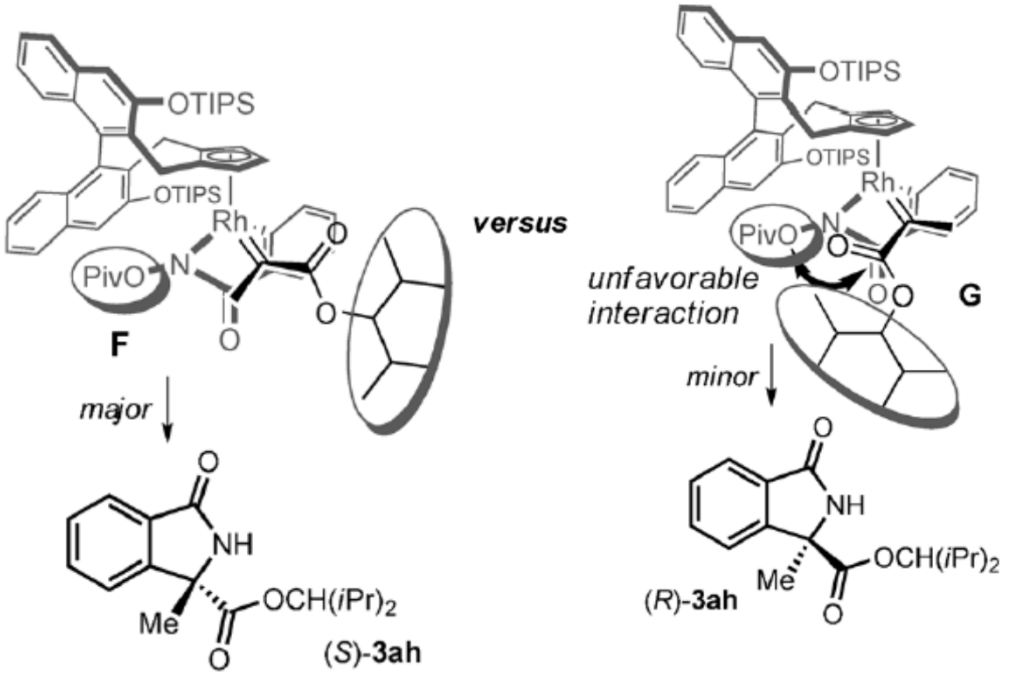


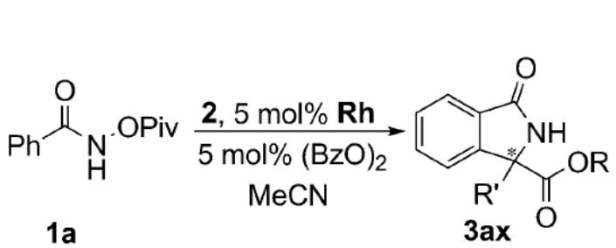
Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 7896

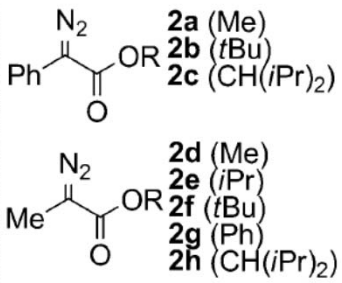
Racemic version reported by Rovis: Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364

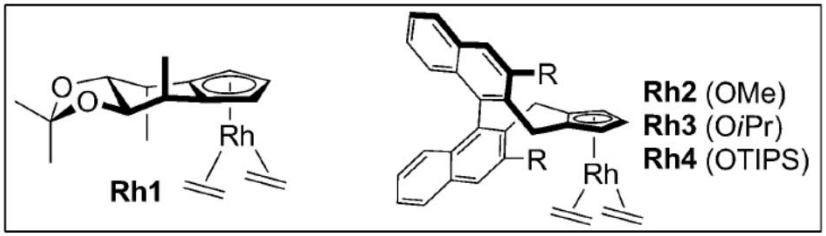


Plausible mode for the enantioselectivity



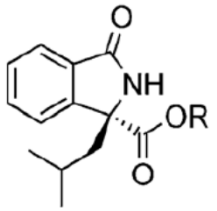




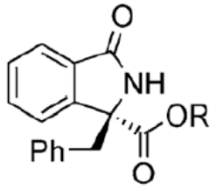


Entry	Rh	Diazo ester **2**	*T* [°C]	Yield [%][b]	e.r.[c]
1	**Rh1**	**2a**	23	80	78:22
2[d]	**Rh2**	**2a**	23	32	86:14
3	**Rh2**	**2a**	50	83	81.5:18.5
4	**Rh2**	**2b**	50	83	52:48
5	**Rh2**	**2c**	50	83	55.5:44.5
6	**Rh2**	**2d**	35	17	81:19
7	**Rh2**	**2e**	35	50	87:13
8	**Rh2**	**2f**	35	48	89:11
9	**Rh2**	**2g**	35	60	88:12
10	**Rh2**	**2h**	35	91	93:7
11	**Rh1**	**2h**	35	75	85.5:14.5
12	**Rh3**	**2h**	35	83	90:10
13	**Rh4**	**2h**	35	75	96:4
14	**Rh4**	**2h**	**23**	**84 (83)**	**96.5:3.5**
15[e]	**Rh4**	**2h**	23	60	95.5:4.5
16[f]	**Rh4**	**2h**	23	35	95.5:4.5

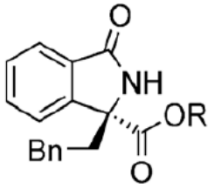
Scope of the diazo compounds



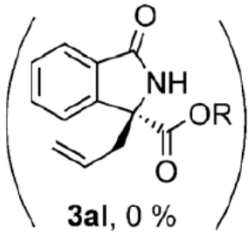
3ai,[a] 69%, 95:5 e.r.



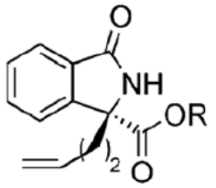
3aj,[a,c] 74%, 94.5:5.5 e.r.



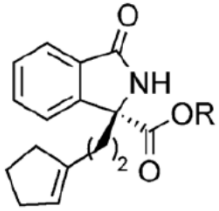
3ak,[a] 79%, 93.5:6.5 e.r.



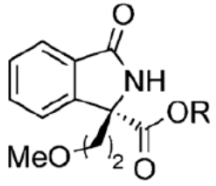
3al, 0 %



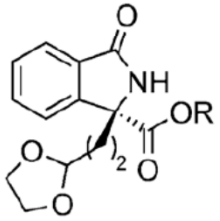
3am,[b] 52%, 92.5:7.5 e.r.



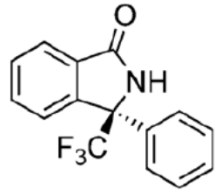
3an,[a] 76%, 94.5:5.5 e.r.



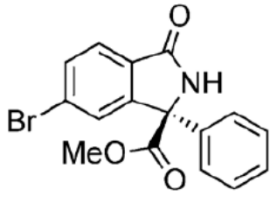
3ao, 84%, 96.5:3.5 e.r.



3ap, 61%, 94.5:5.5 e.r.

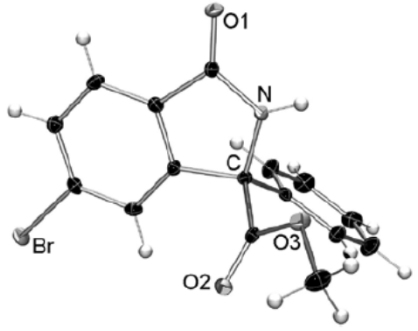


3aq,[b,d] 94%, 79.5:20.5 e.r.

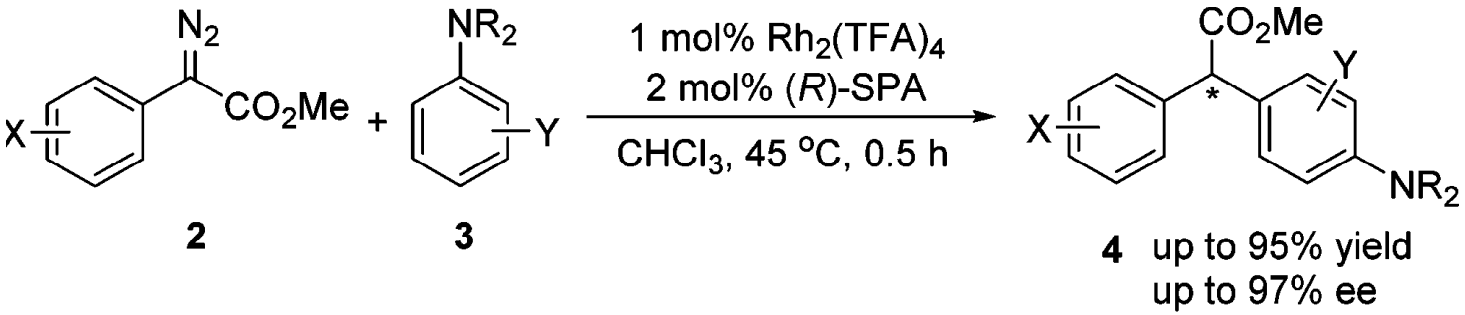


3ja,[b,c] 81%, 78:22 e.r.

≡

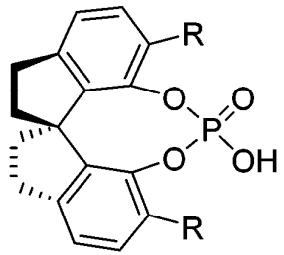


Enantioselective C(sp^2)-H Insertion of Aniline Derivatives with Diazo Cpds



2 **3**

4 up to 95% yield
up to 97% ee

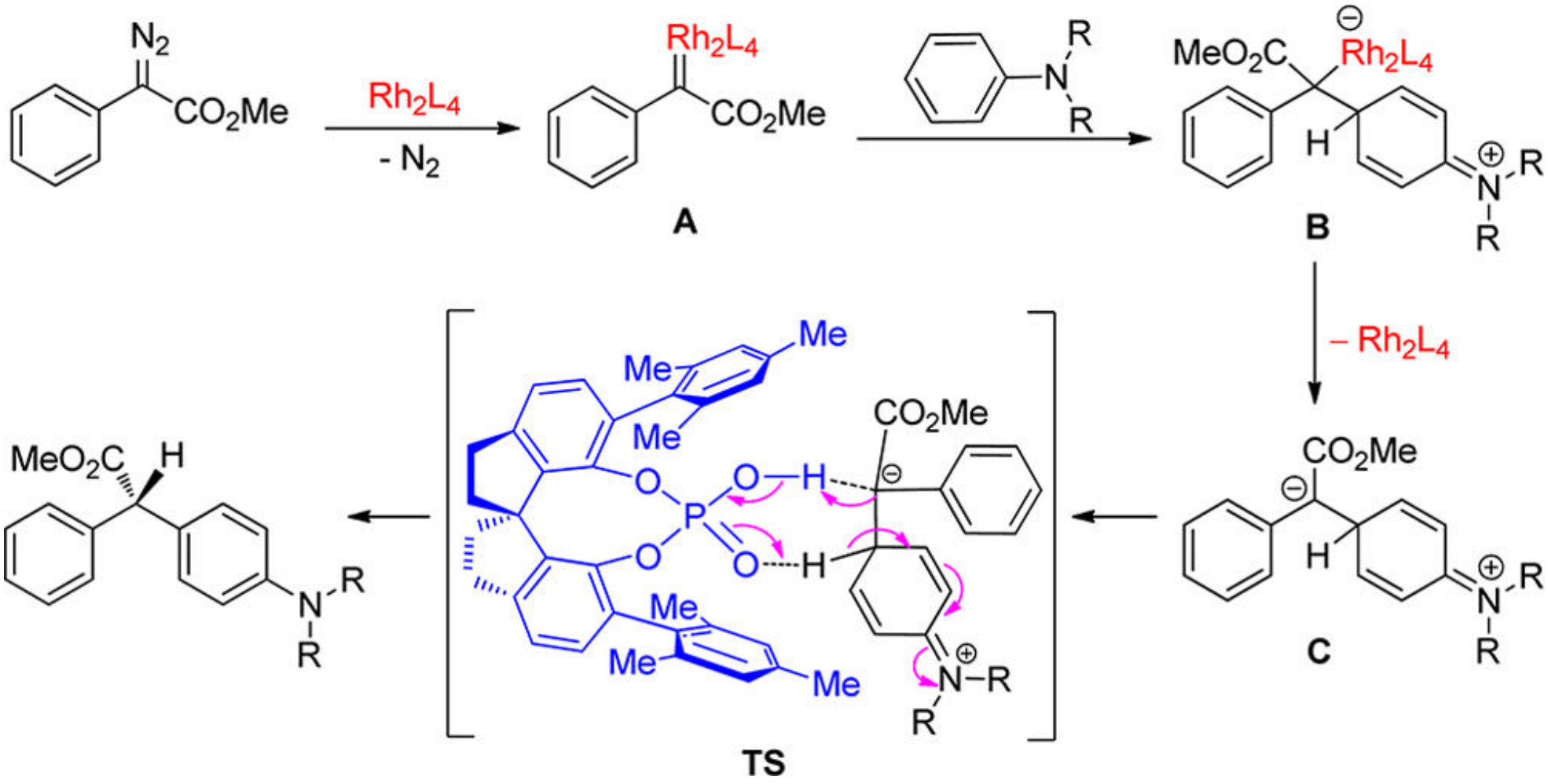


(*R*)-SPA (**1**)

1a R = Ph
1b R = 4-$NO_2C_6H_4$
1c R = 4-PhC_6H_4
1d R = 3,5-$(Me)_2C_6H_3$
1e R = 3,5-$(Ph)_2C_6H_3$
1f R = 2-Naphthyl
1g R = 2,4,6-$(Me)_3C_6H_2$
1h R = 2,4,6-$(^iPr)_3C_6H_2$

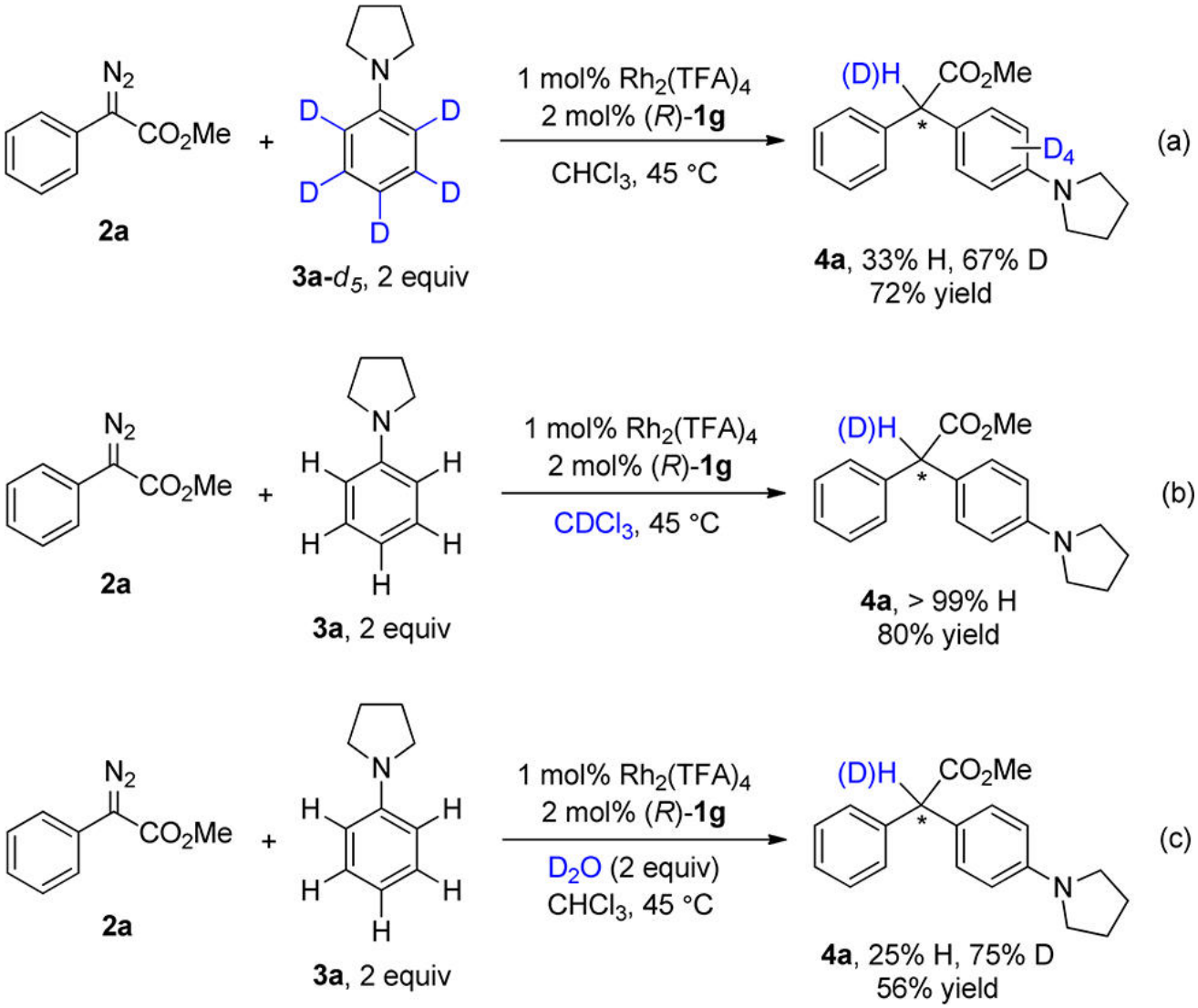
Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700

Proposed Pathway for this transformation



Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700

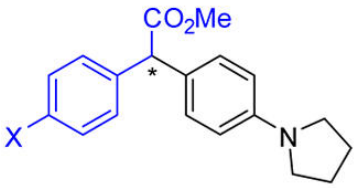
Mechanism Studies



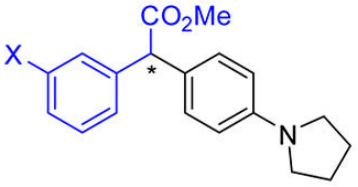
Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700

Substrate Scope

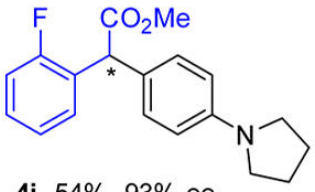
Scope of Diazo Cpds



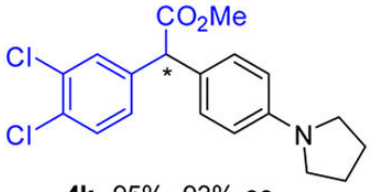
4a, X = H, 79%, 97% ee
4b, X = CF_3, 86%, 93% ee
4c, X = Cl, 89%, 93% ee
4d, X = Br, 90%, 96% ee
4e, X = MeO, 66%, 93% ee
4f, X = ^{t}Bu, 68%, 93% ee
4g, X = Ph, 82%, 96% ee



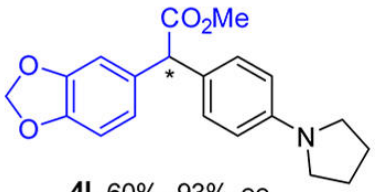
4h, X = F, 86%, 94% ee
4i, X = MeO, 75%, 94% ee



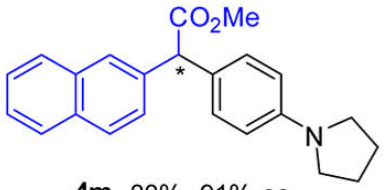
4j, 54%, 93% ee



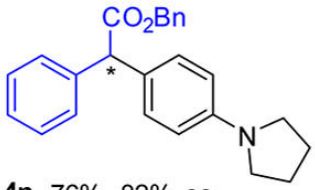
4k, 95%, 93% ee



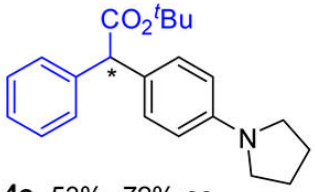
4l, 60%, 93% ee



4m, 80%, 91% ee

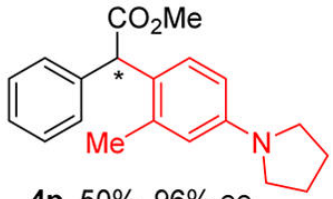


4n, 76%, 82% ee

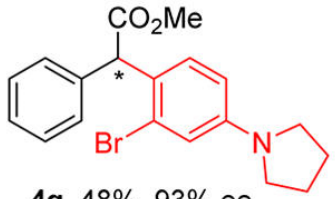


4o, 53%, 72% ee

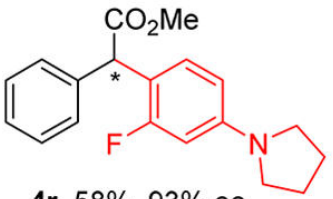
Scope of Aniline Substrates



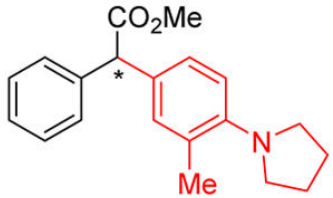
4p, 50%, 96% ee



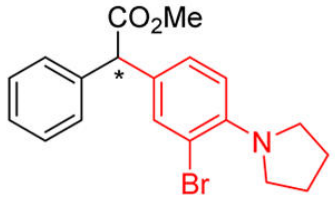
4q, 48%, 93% ee



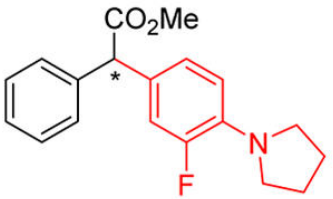
4r, 58%, 93% ee



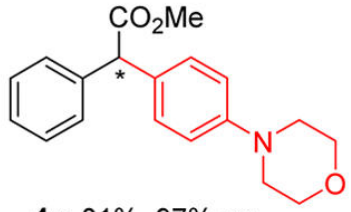
4s, 54%, 58% ee



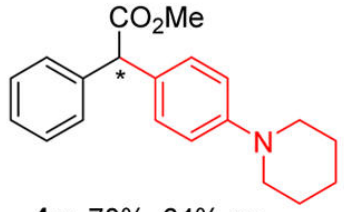
4t, 68%, 94% ee



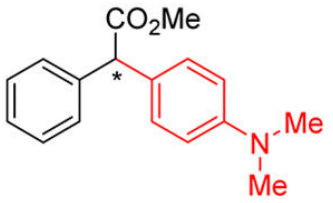
4u, 75%, 91% ee



4v, 81%, 97% ee



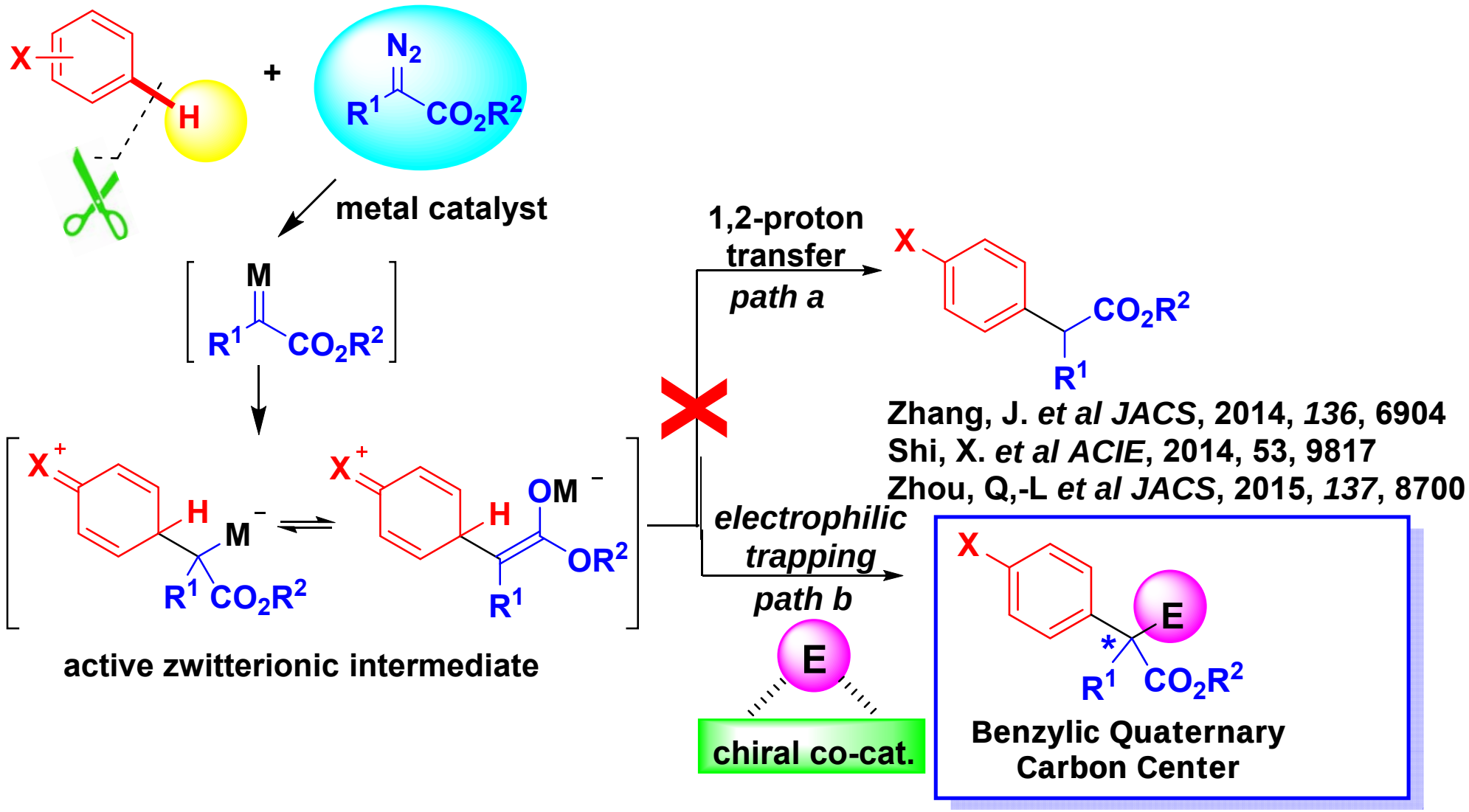
4w, 78%, 64% ee



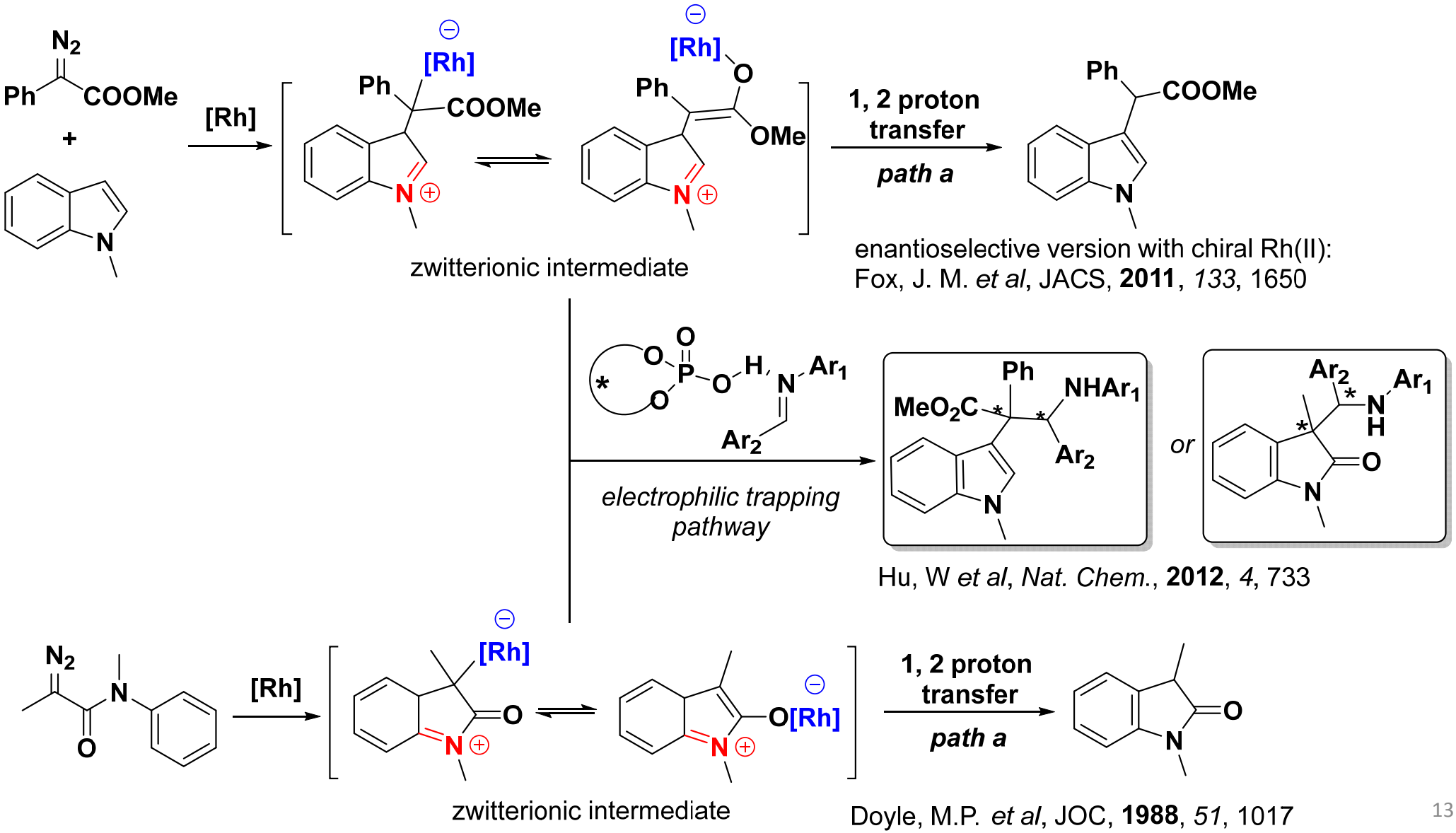
4x, 71%, 59% ee

Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700

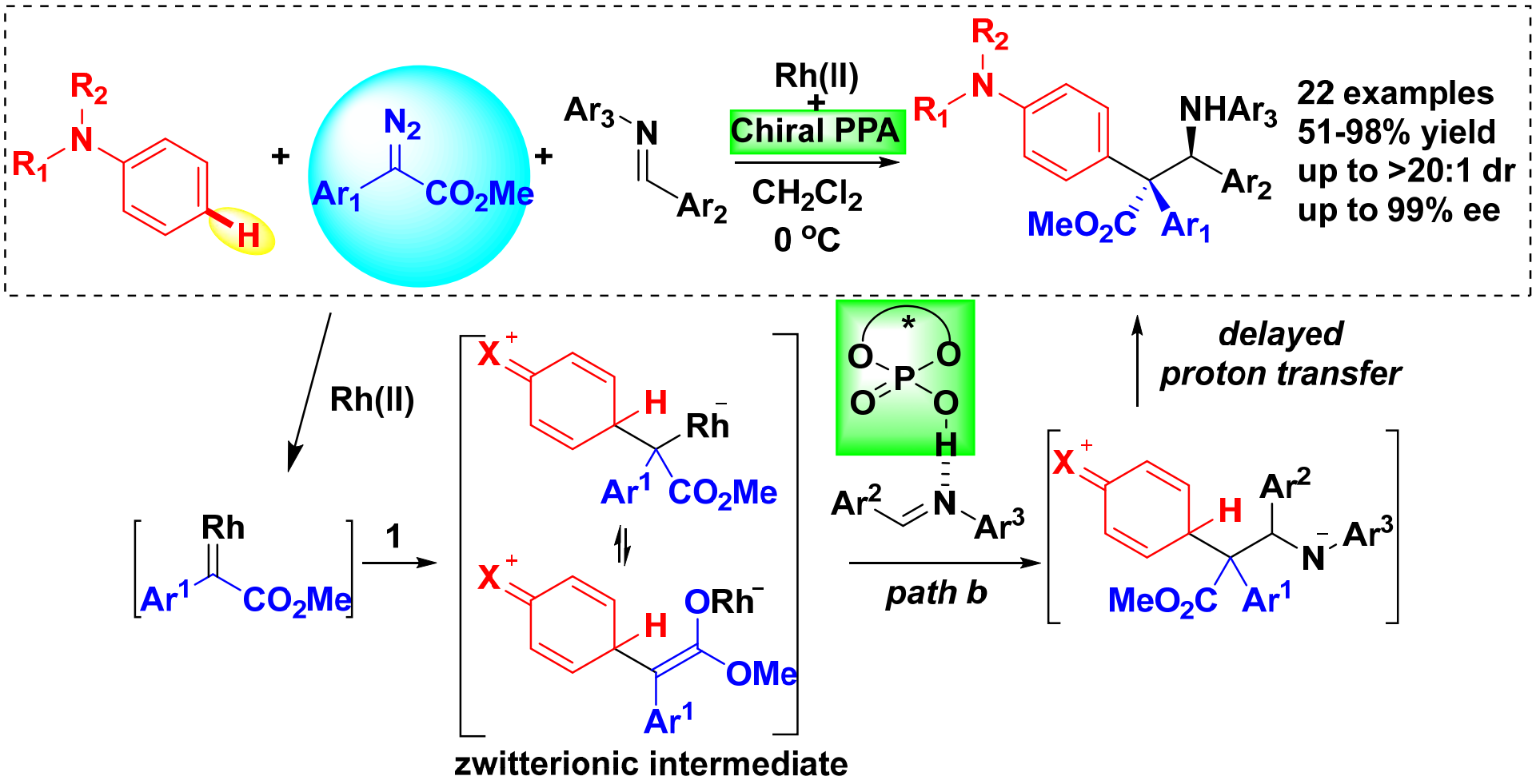
Our Design—
Electrophilic Interception of the Zwitterionic Intermediate



Precedent—Using Indole & N-Phenyl Diazoamide as Zwitterionic Precursor



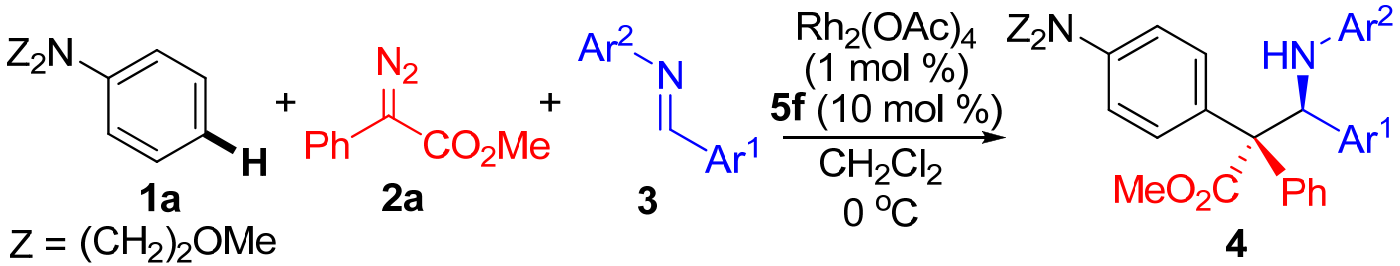
Using Imine as the Electophile & Rh&Chiral PPA Co-Cat. System



Jia, S.; **Xing, D.***; Zhang, D.; Hu, W.* *Angew. Chem. Int. Ed.*, **2014**, *53*, 13098

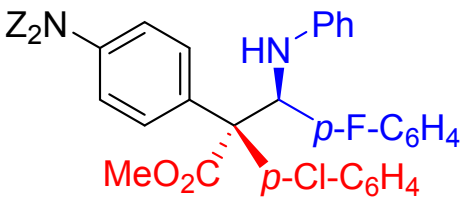
Synfacts, **2014,** *10(11)*, 1171

Substrate Scope-1

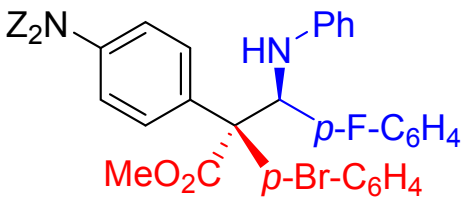


entry	3	Ar^1/Ar^2	4	yield (%)[b]	dr[c]	ee (%)[d]
1	3a	*p*-Cl-C_6H_4/Ph	4a	74	91:9	99
2	3b	*p*-Br-C_6H_4/Ph	4b	68	92:8	98
3	3c	*p*-F-C_6H_4/Ph	4c	67	91:9	99
4	3d	*p*-CF_3-C_6H_4/Ph	4d	68	87:13	98
5	3e	3,4-Cl_2-C_6H_3/Ph	4e	73	95:5	90
6	3f	Ph/Ph	4f	57	88:12	96
7	3g	*p*-Me-C_6H_4/Ph	4g	43	82:18	98
8	3h	*p*-F-C_6H_4/*p*-Cl-C_6H_4	4h	68	86:14	99
9	3i	*p*-Cl-C_6H_4/*p*-Br-C_6H_4	4i	57	85:15	99
10	3j	Ph/*m*-Br--C_6H_4	4j	56	80:20	97

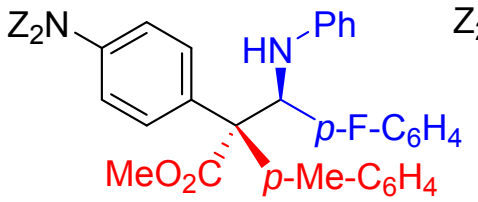
Substrate Scope-2



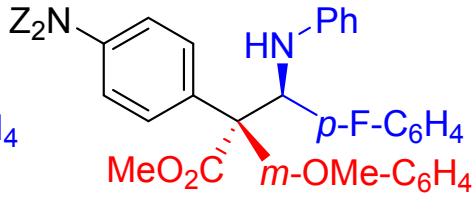
4k
84%
90:10 dr; 99% ee



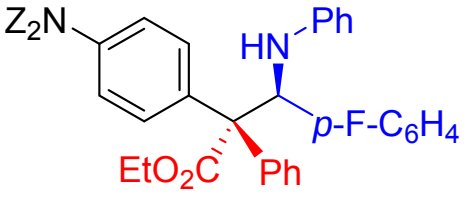
4l
83%
90:10 dr; 99% ee



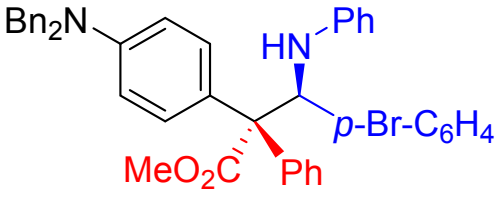
4m
71%
91:9 dr; 99% ee



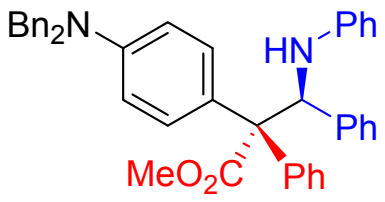
4n
79%
92:8 dr; 98% ee



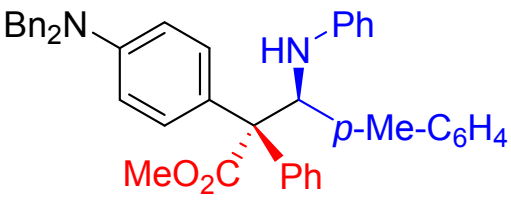
4o
40%
78:22 dr; 97% ee



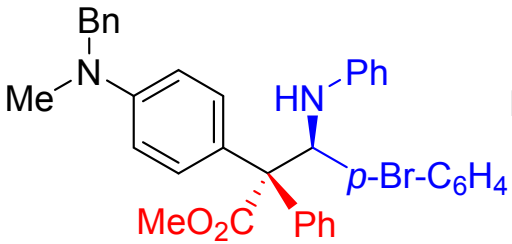
4p
71%
95:5 dr; 99% ee



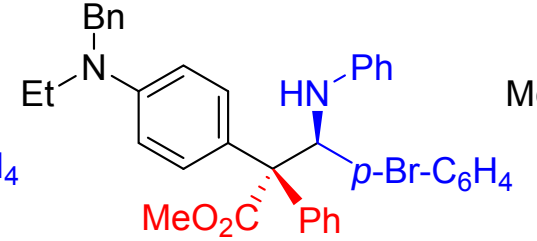
4q
58%
95:5 dr; 99% ee



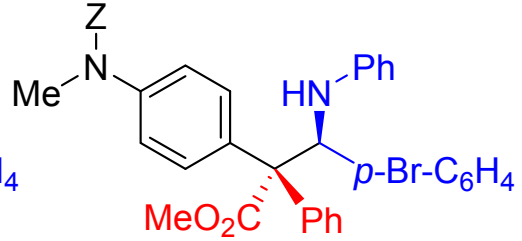
4r
51%
95:5 dr; 97% ee



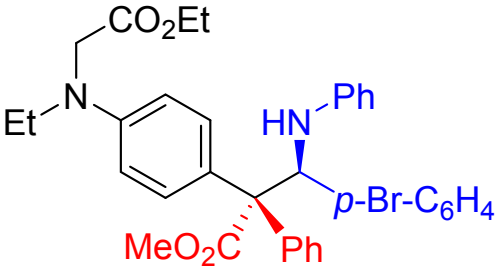
4s
68%
90:10 dr; 98% ee



4t
74%
91:9 dr; 98% ee



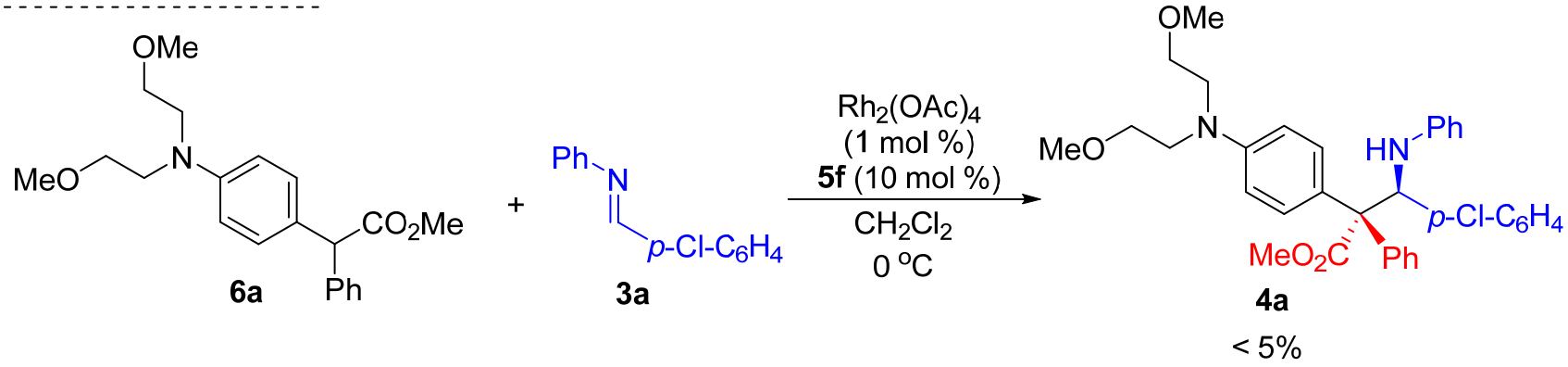
4u
55%
88:12 dr; 99% ee



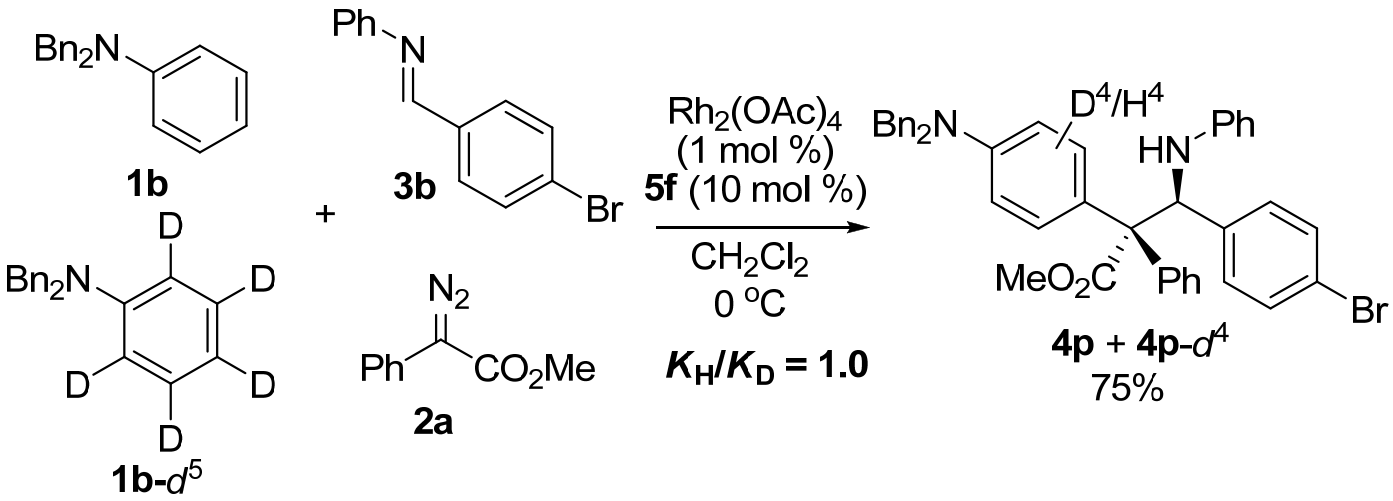
4v
73%
90:10 dr; 99% ee

Control Expt. & Intermolecular KIE

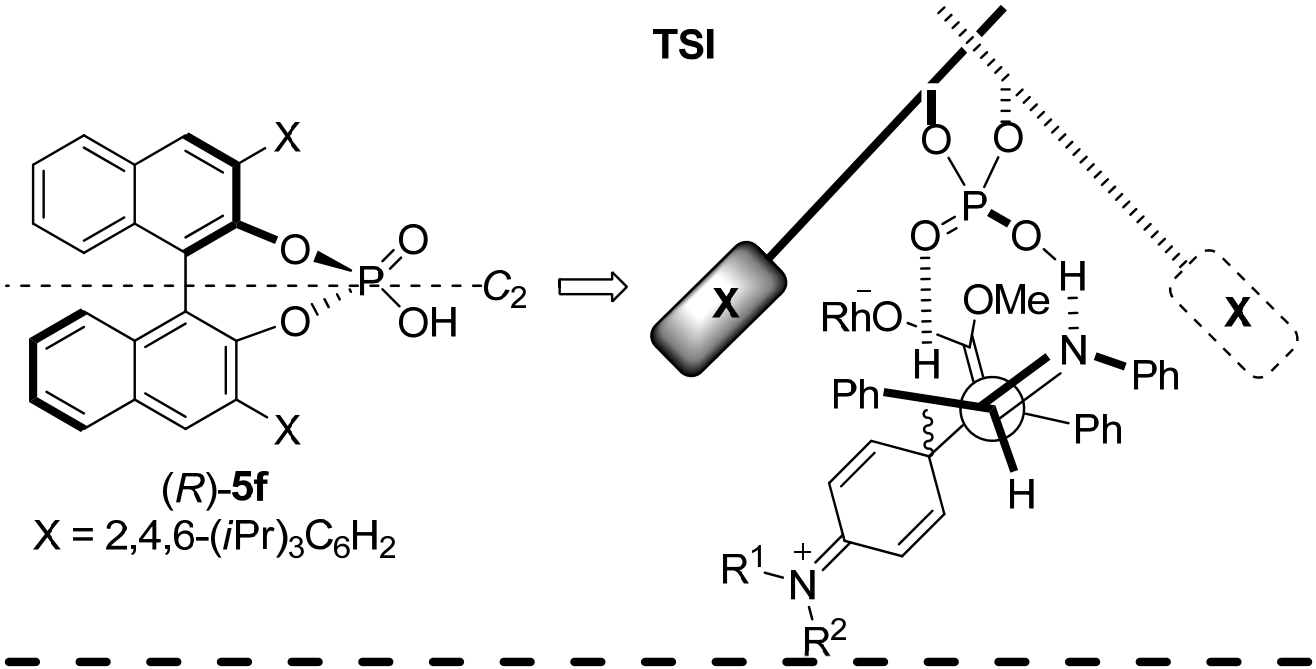
Control Experiment

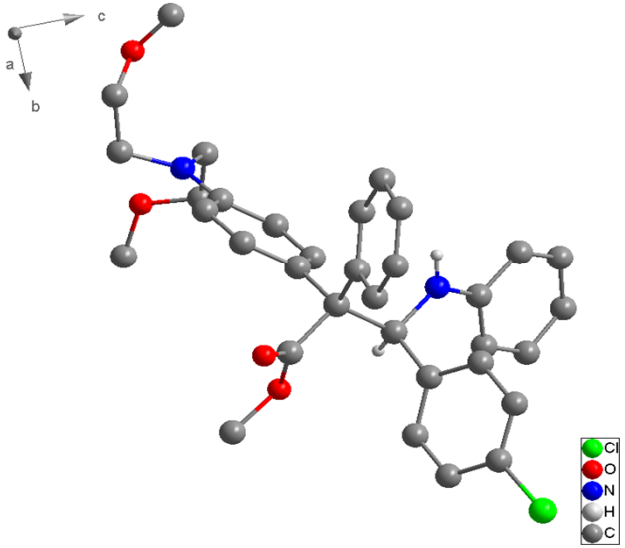


Intermolecular KIE

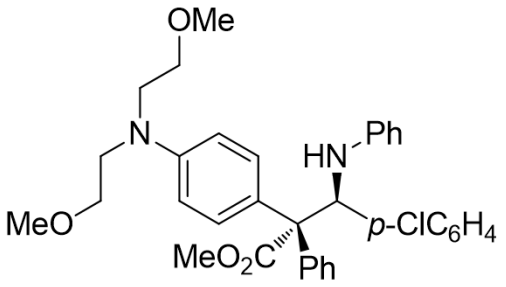


Proposed Transition State



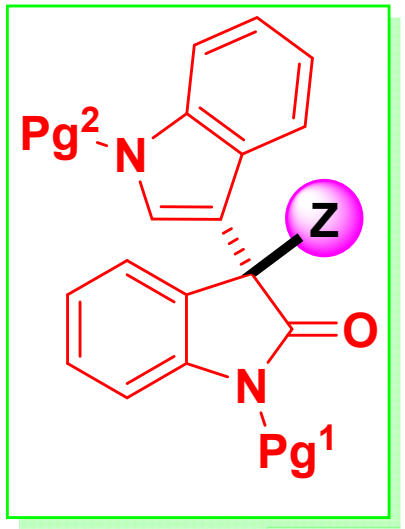


≡

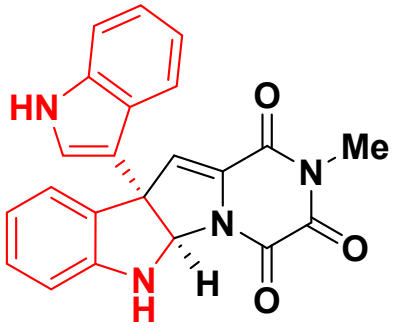


(2*R*,3*S*)-*anti*-**4a**

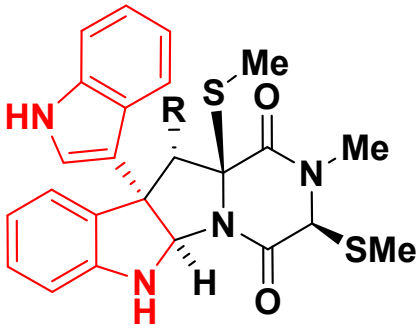
“Electrophilic Trapping” Protocol for Synthesis of Mixed 3,3’-Bisoxindoles



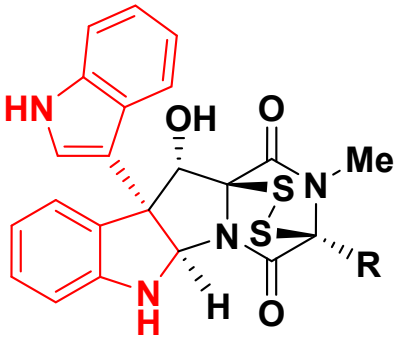
Z: carbon substituent



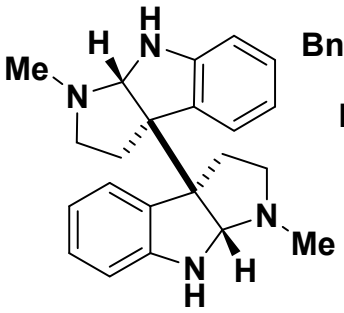
(+)-gliocladin C



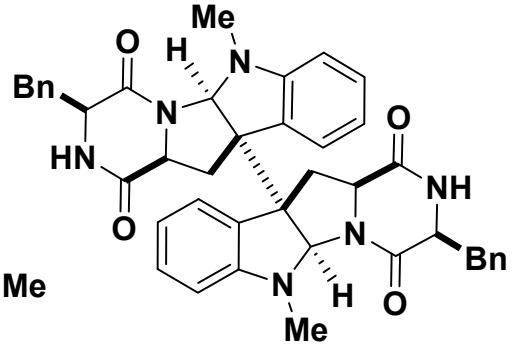
(+)-gliocladin A, R = OH
(+)-gliocladin B, R = H



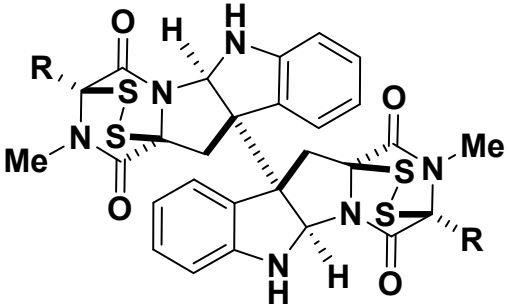
(+)-bionectin A, R = H
(+)-gliocladine C, R = Me
(+)-leptosin D, R = *i*-Pr
(+)-T988A, R = CH_2OH
(+)-bionectin B, R = CH(OH)Me



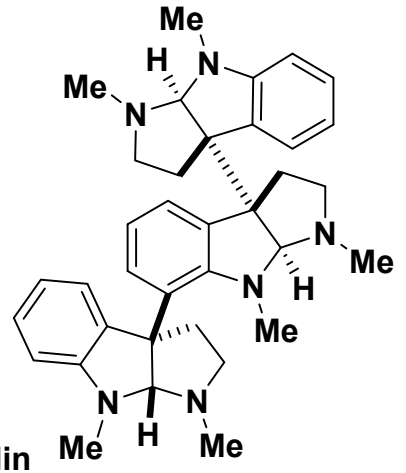
(-)-Chimonanthine



(+)-WIN 64821

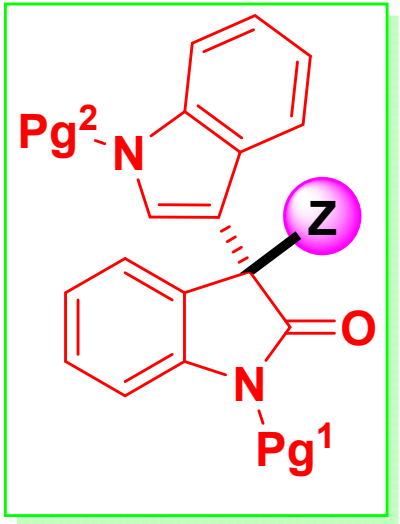


R = Me, (+)-dideoxyverticillin
R = CH_2OH, (+)-chaetocin

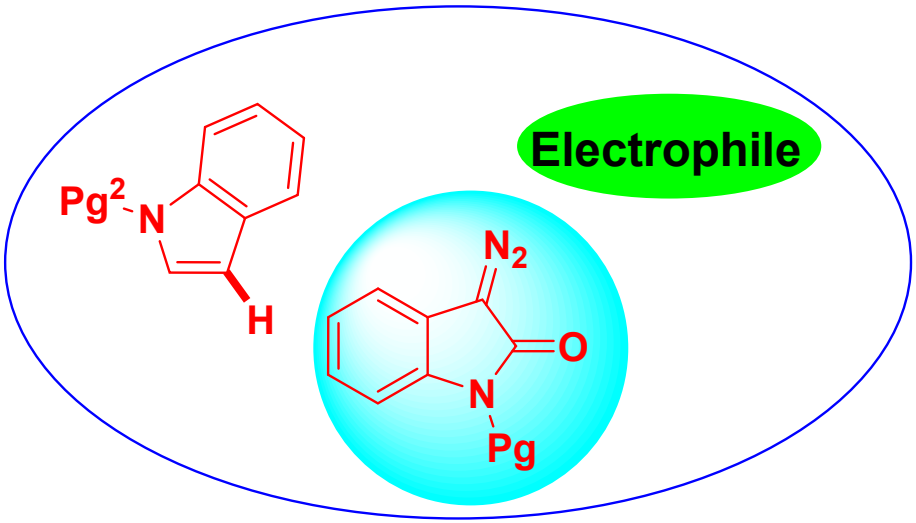


(-)-idiospermuline

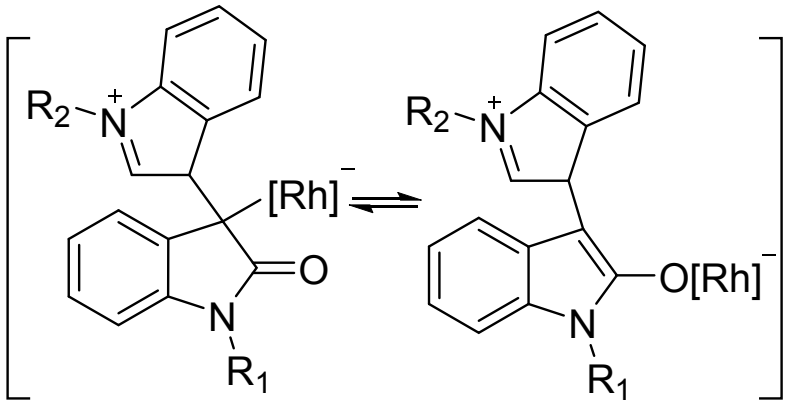
“Electrophilic Trapping” Protocol for Synthesis of Mixed 3,3’-Bisoxindoles



Z: carbon substituent

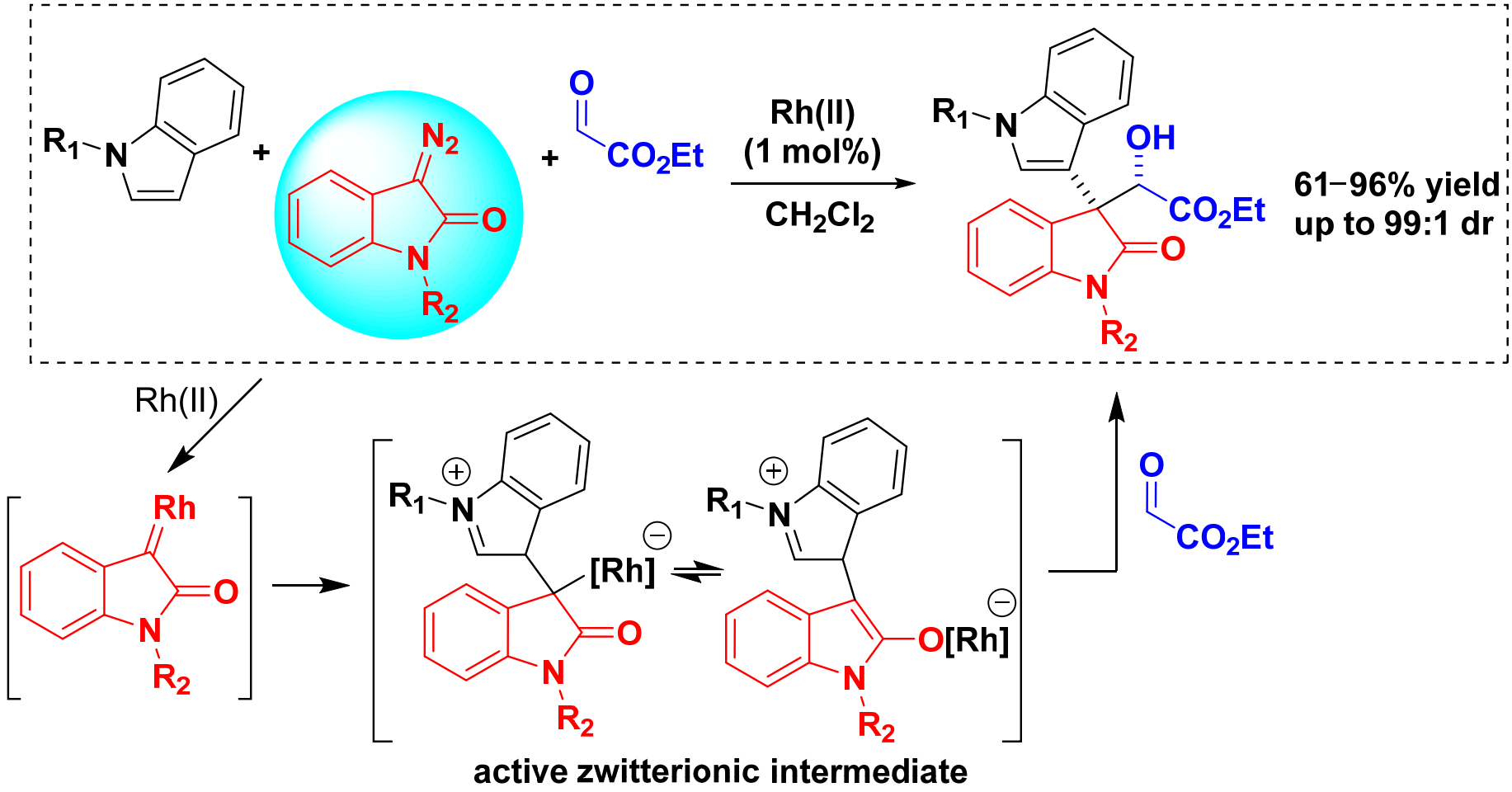


via



zwitterionic intermediate

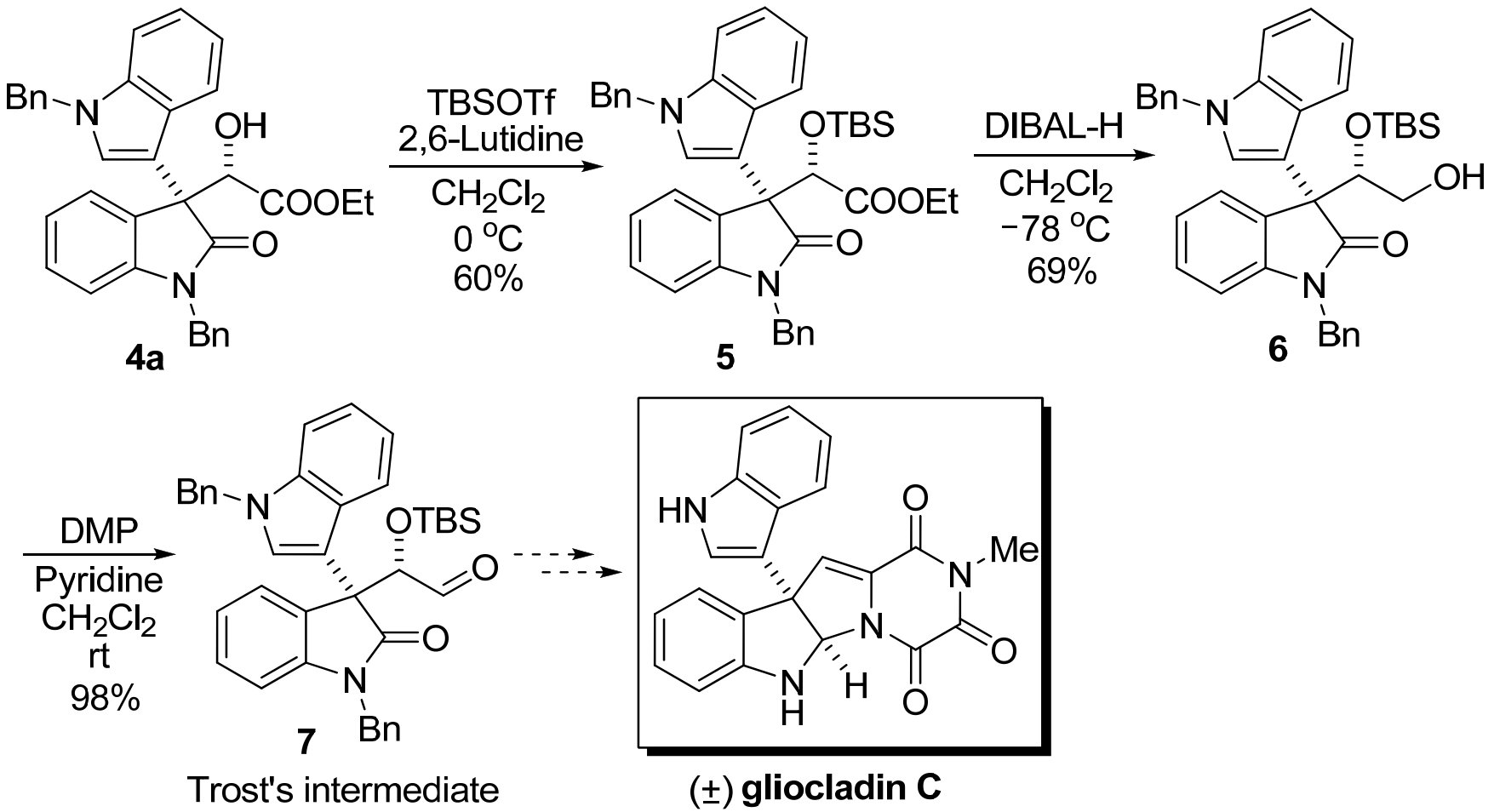
Using Ethyl Glyoxylate as the Electrophile



Xing, D.*; Jing, C.; Li, X.; Qiu, H.; Hu, W.* *Org. Lett.* **2013**, *15*, 3578.

Synfacts, **2013,** *9(10)*, 1078

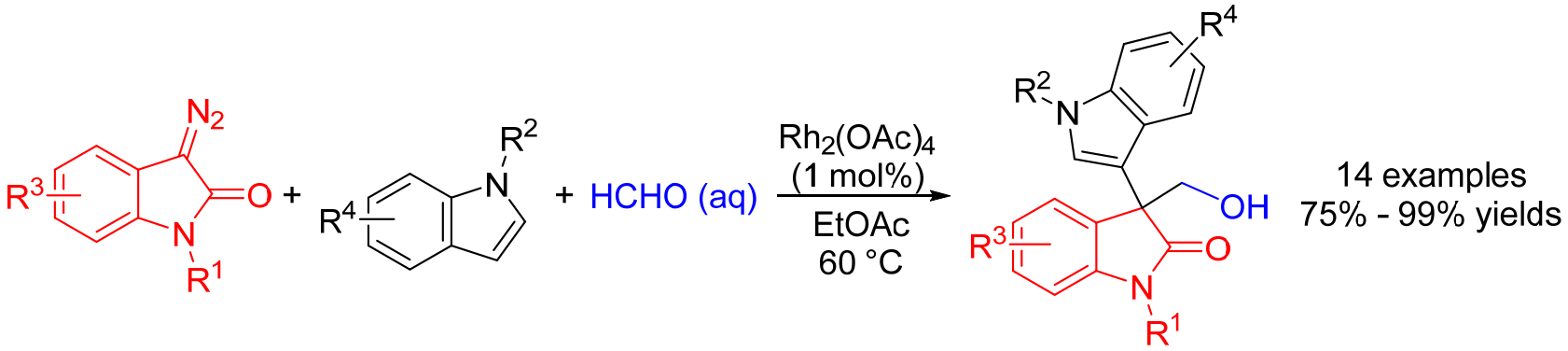
Synthetic Applications

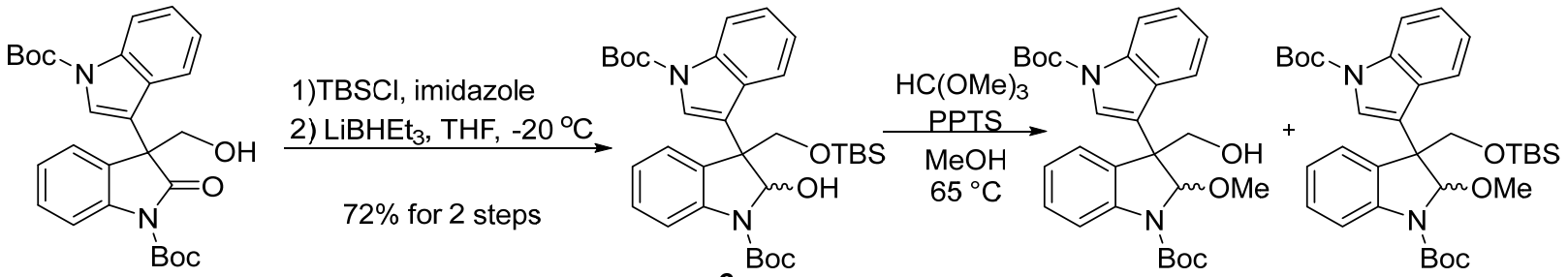


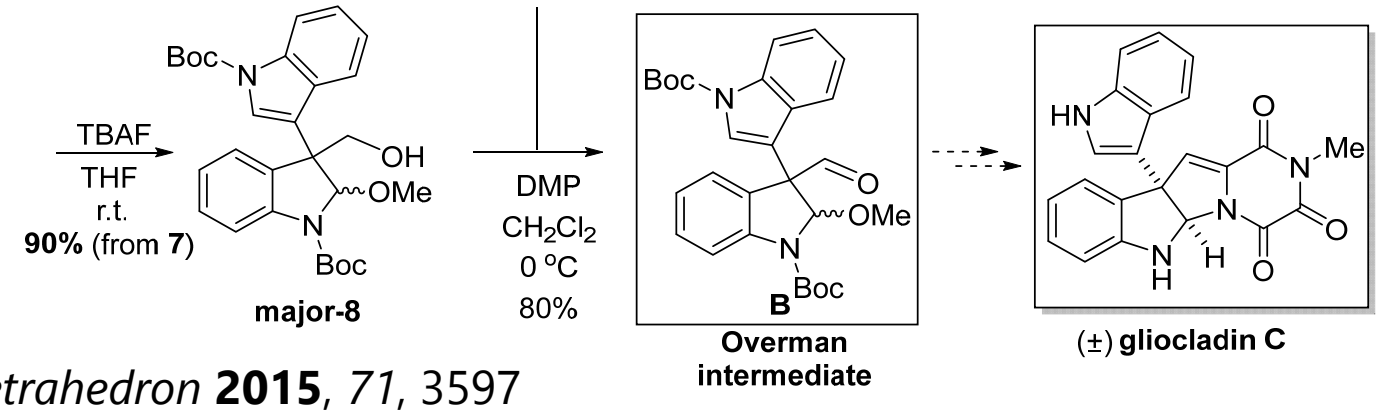
Xing, D.*; Jing, C.; Li, X.; Qiu, H.; Hu, W.* *Org. Lett.* **2013**, *15*, 3578.

Synfacts, **2013,** *9(10)*, 1078

Using Formaldehyde as Electrophile

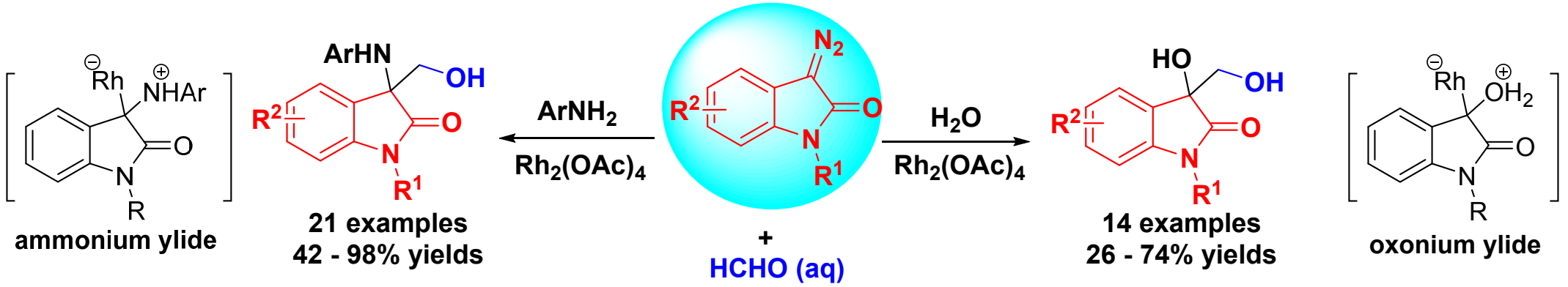


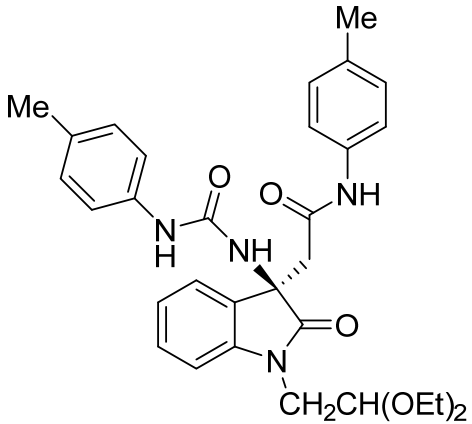


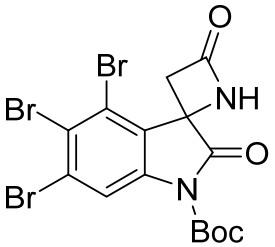


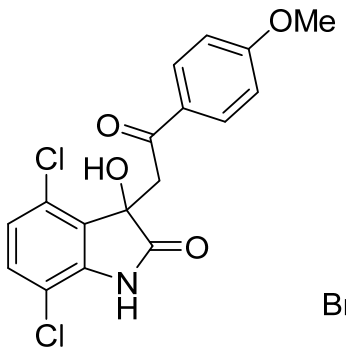
Jing, C.; **Xing, D.***; Wang, C.; Hu, W.* *Tetrahedron* **2015**, *71*, 3597

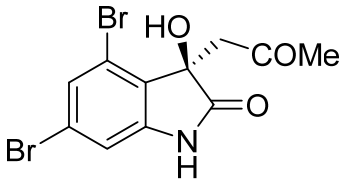
Using Formaldehyde as Electrophile





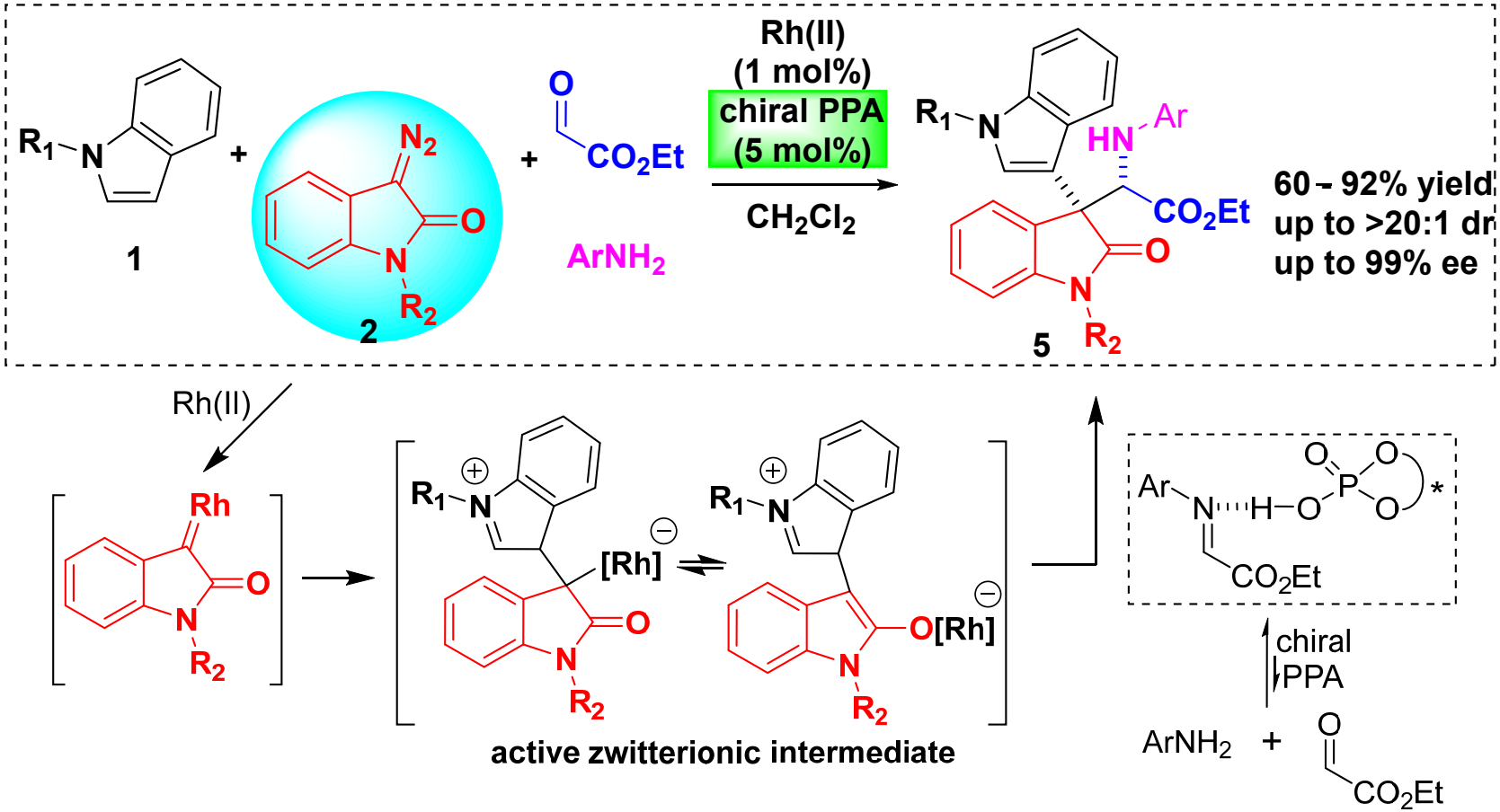






Wang, C.; **Xing, D.***; Wang, D.; Wu, X.; Hu, W.* *J. Org. Chem.* **2014**, *79*, 3908

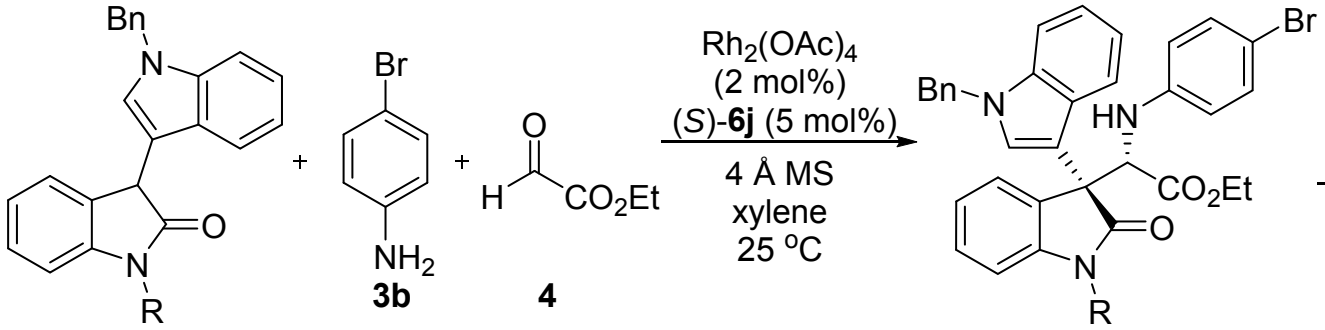
Using in situ Generated Iminoester as the Electrophile



Jing, C.; **Xing, D.***; Hu, W.* *Org. Lett.* **2015**, *17*, 4336

Using in situ Generated Iminoester as the Electrophile

Control Experiment

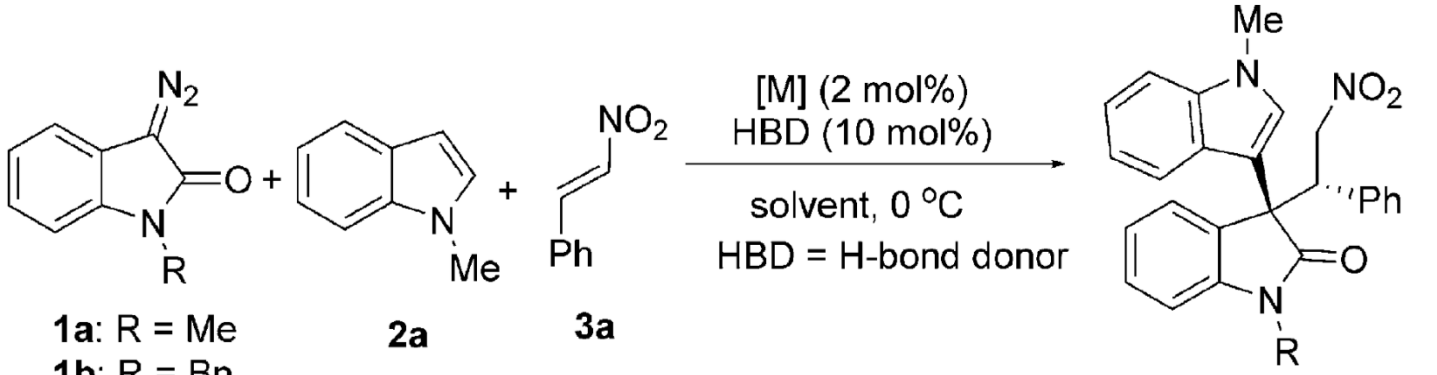


7a (R = Boc)
7r (R = Bn)

1 h:
5b (R = Boc): 13% yield, >95:5 d.r., 14% ee
5r (R= Bn): < 5%

20 h:
5b (R = Boc): 92% yield, >95:5 d.r., 67% ee
5r (R= Bn): 12% yield, >95:5 d.r., 57% ee

As a comparation, Gong's similar work follows a stepwise pathway

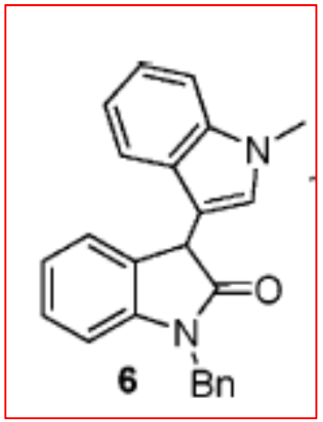


1a: R = Me
1b: R = Bn

2a

3a

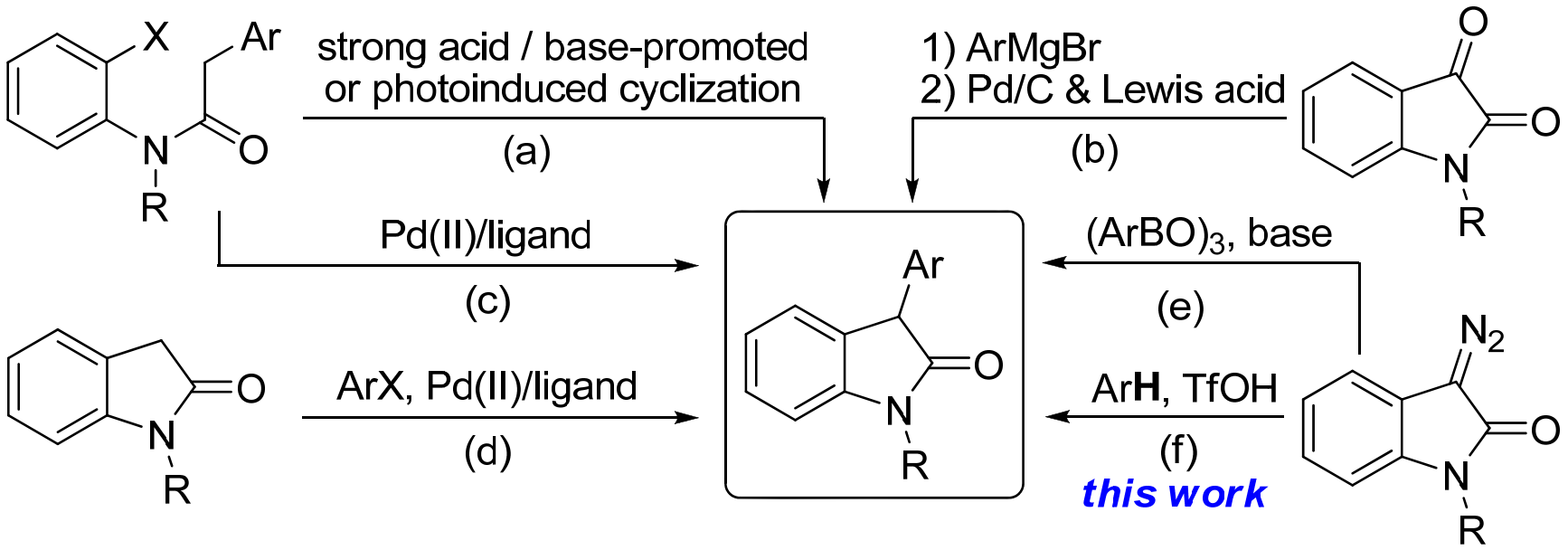
5a: R = Me; **5b**: R = Bn

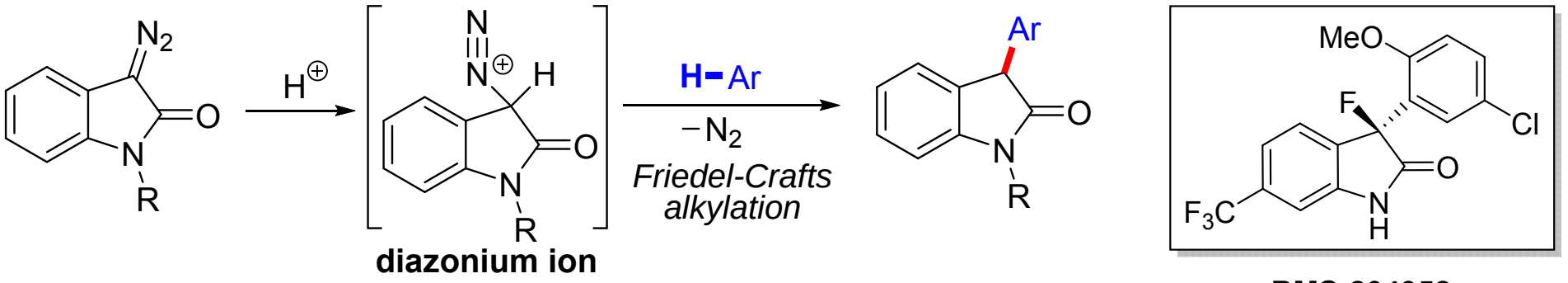


6

Gong, L.-Z. *et al Angew. Chem. Int. Ed.* **2014**, *53*, 10763.

Metal-Free Synthesis of 3-Aryloxindoles

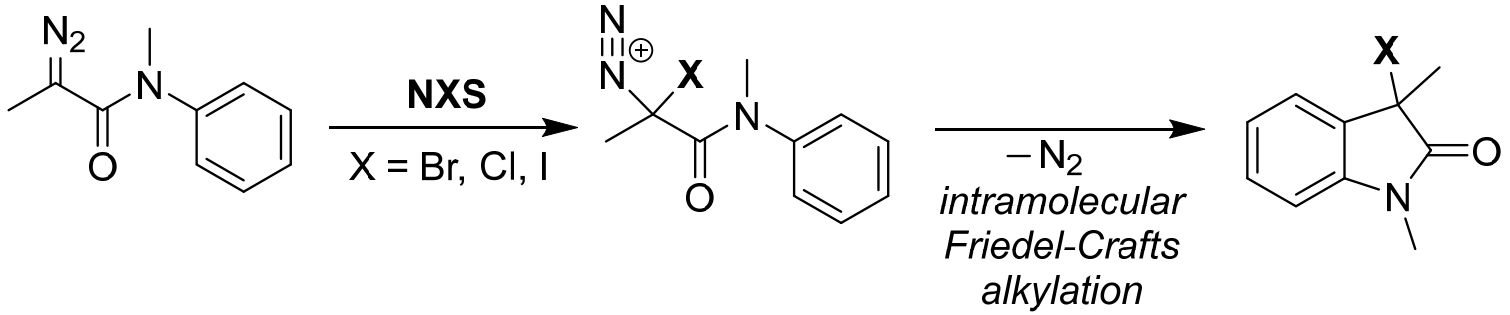


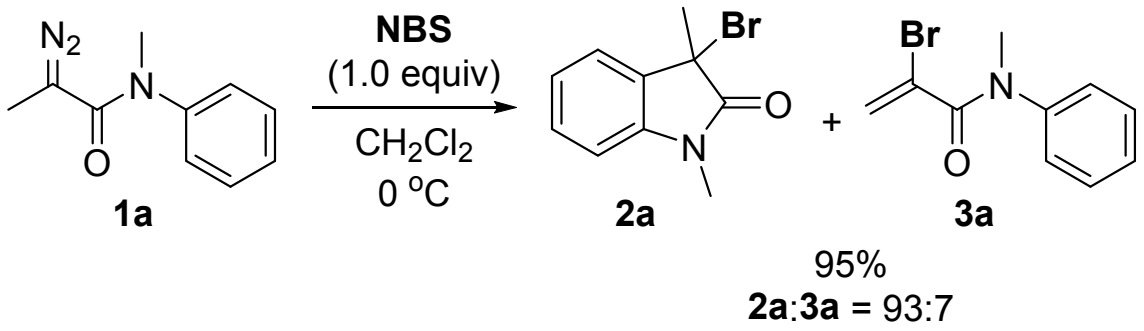


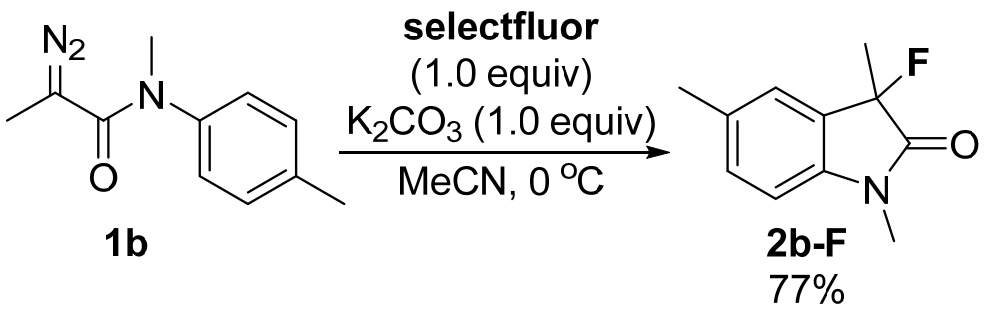
BMS-204352
MaxiPost™

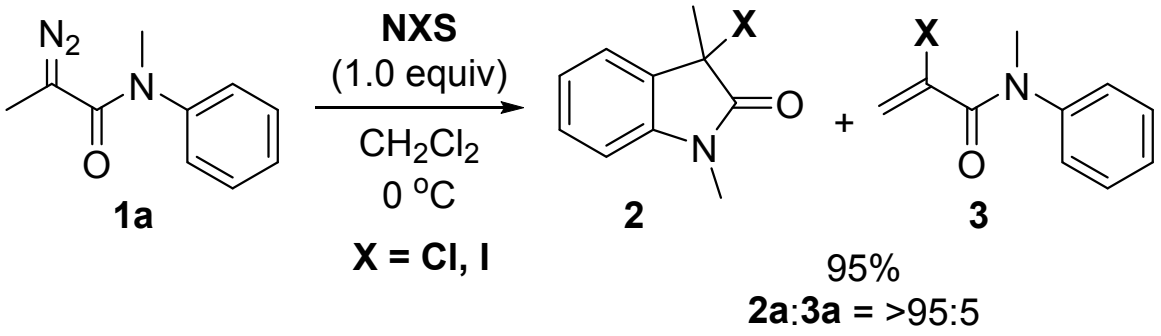
Zhai, C.;. **Xing, D.***; Jing, C.; Zhou, J.; Wang, C.; Wang, D.; Hu, W.* *Org. Lett.* **2014**, *16*, 2934

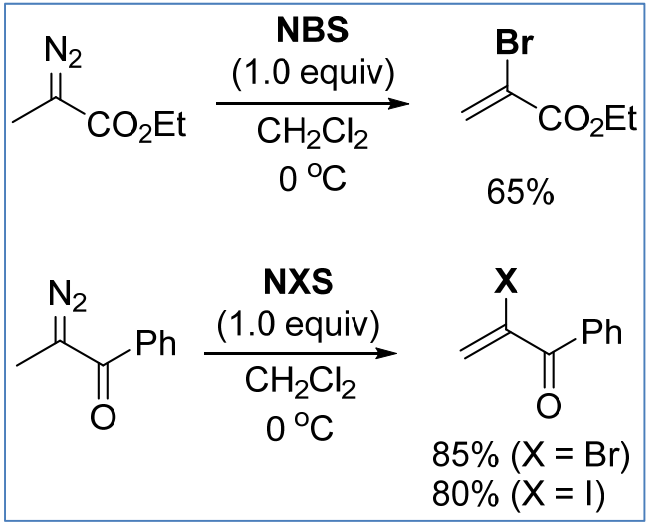
Metal-Free Synthesis of 3-Halooxindoles





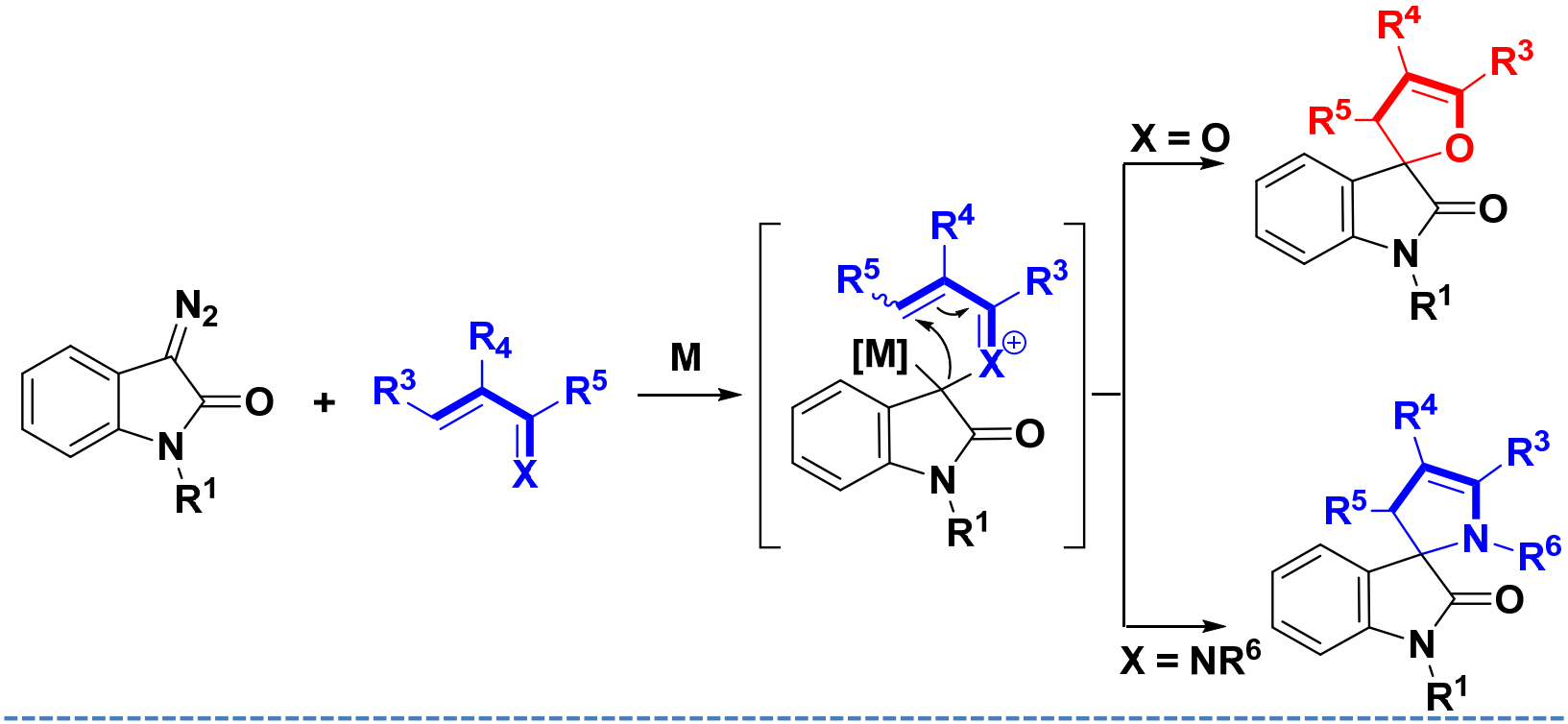


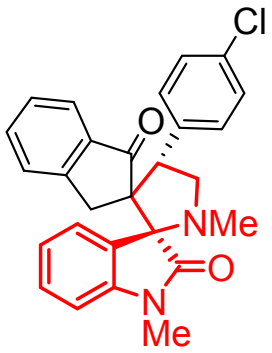




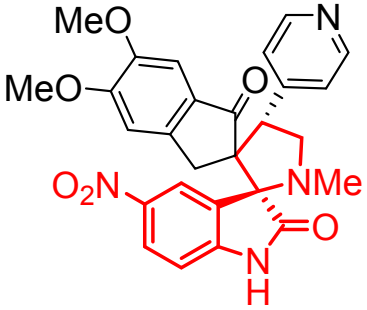
Unpublished results

Proposed [4+1] Cycloaddition of 3-Diazoxindole

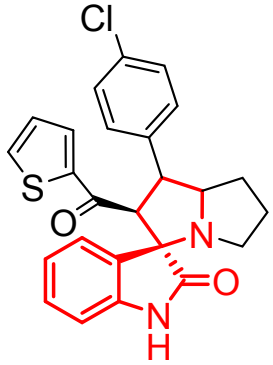




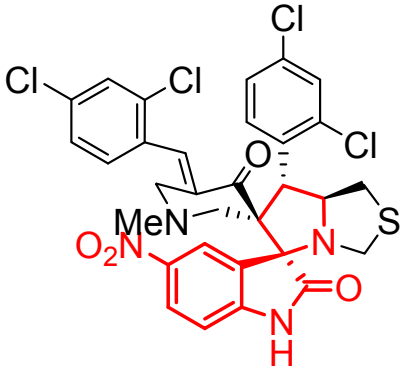
anti-tumor



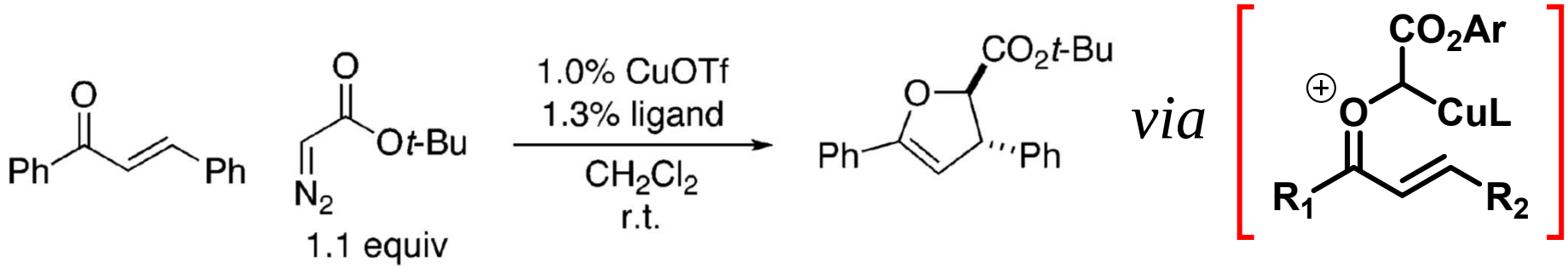
acetylcholinesterase (AChE) inhibitory



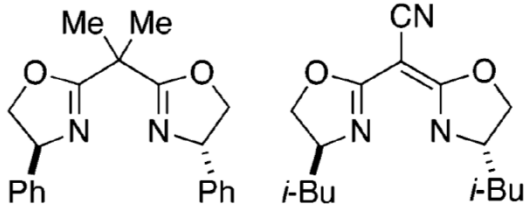
anti-bacterial



anti-tubercular

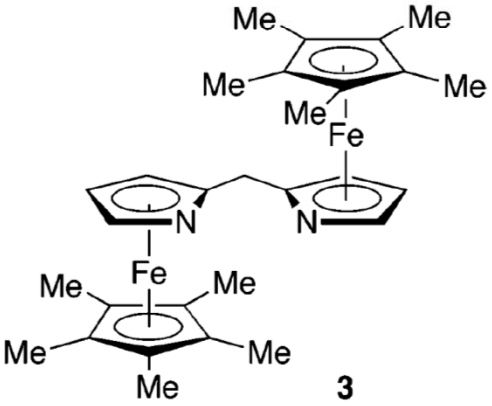


entry	ligand	yield (%)[b]	dr	ee (%)
1	bis(oxazoline) **1**	12	>20:1	−20[c]
2	semicorrin **2**	<2		
3	bis(azaferrocene) **3**	6	>20:1	34
4	(−)-bpy*	45	>20:1	60
5	no ligand	10	>20:1	
6	no CuOTf, no ligand	<2		

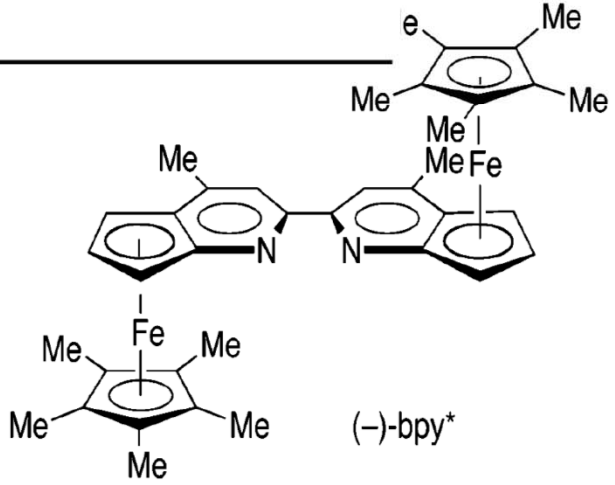


1

2

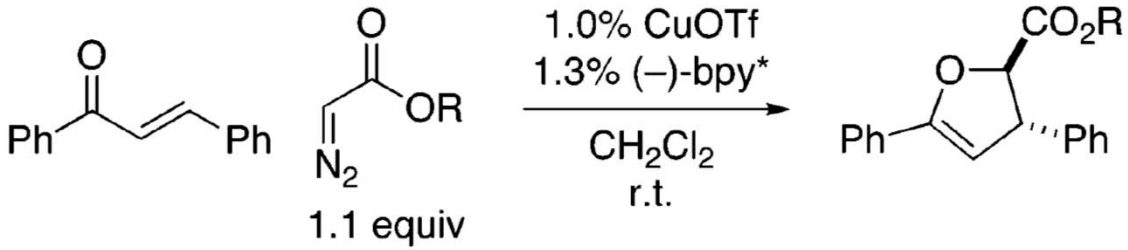


3

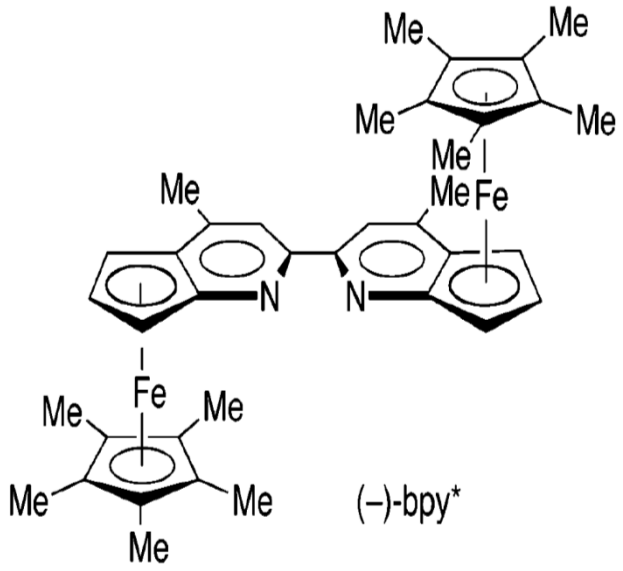


(–)-bpy*

Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046

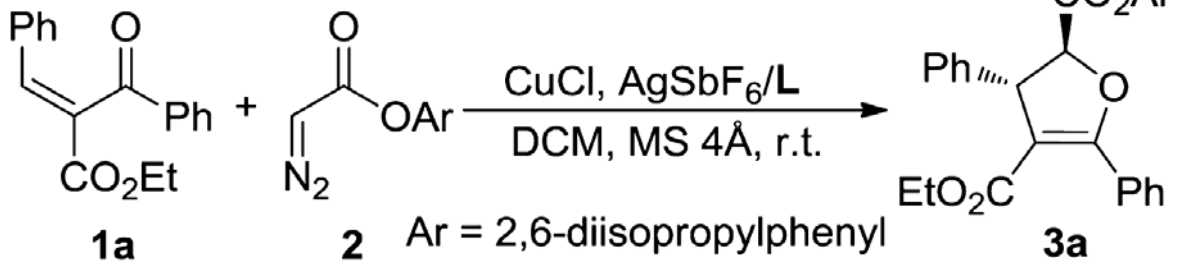


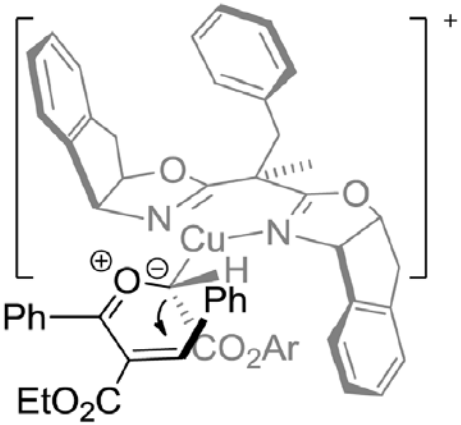
entry	R	yield (%)[b]	dr	ee (%)
1	*t*-Bu	45	>20:1	60
2	Et	43	>20:1	37
3	Ph	44	>20:1	37
4	2,6-dimethylphenyl	63	7:1	83
5	2,6-diisopropylphenyl	79	13:1	85
6	2,6-di-*t*-butyl−4-methylphenyl	47	16:1	85

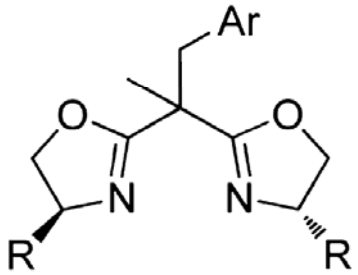


(–)-bpy*

Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046



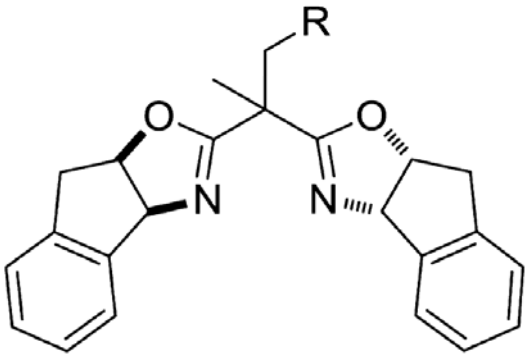




Ar = 3,5-$Me_2C_6H_3$

L2: R = ^{i}Pr

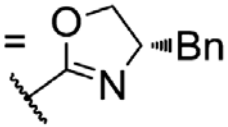
L3: R = ^{t}Bu



L4: R = C_6H_5

L5: R = 3, 5-$(CF_3)_2C_6H_3$

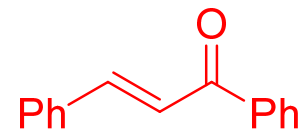
L6: R = 3, 5-$(MeO)_2C_6H_3$

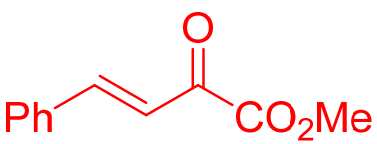
L7: R = 

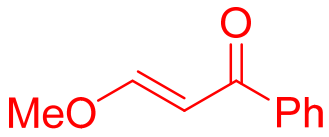
entry	ligand	yield (%)[b]	ee (%)[c]
1	**L2**	94 (94)[d]	91
2	**L3**	45[e]	99
3	**L4**	93 (82)[d]	96
4	**L5**	88	95
5	**L6**	88	84
6	**L7**	86[f]	94

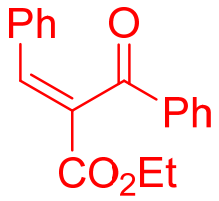
Zhou, J.-L.; Wang, L.-J.; Xu, H.; Sun, X.-L.; Tang, Y. *ACS Cat.* **2013**, *3*, 685

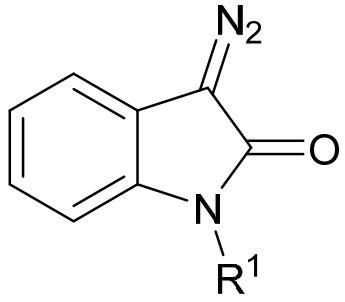
All attempts for the synthesis of dihydrofuran-spirooxindole failed





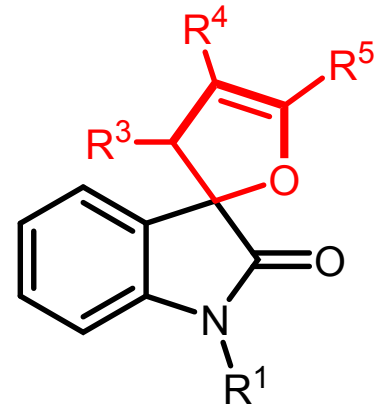




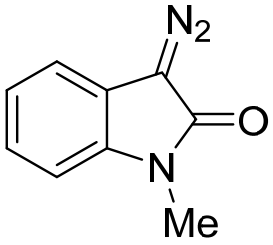


R^1 = Me, Boc, Ts

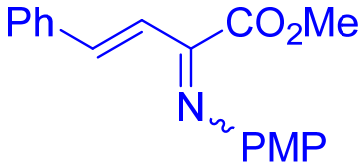
$Rh_2(OAc)_4$, chiral Rh(II), Cu(I)/BOX, Cu(II)/BOX



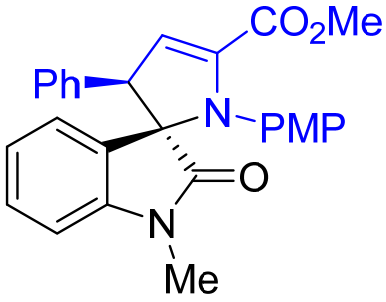
Development for the synthesis of 2-pyrrolin-spirooxindole



+

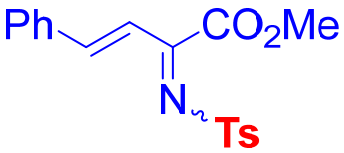


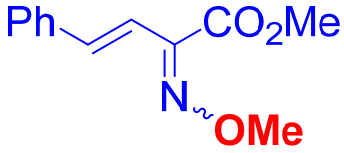
$Rh_2(OAc)_4$
(2 mol%)
4 Å MS
CH_2Cl_2
40 °C

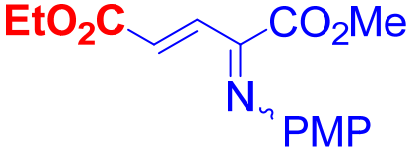


64%
dr >95:5

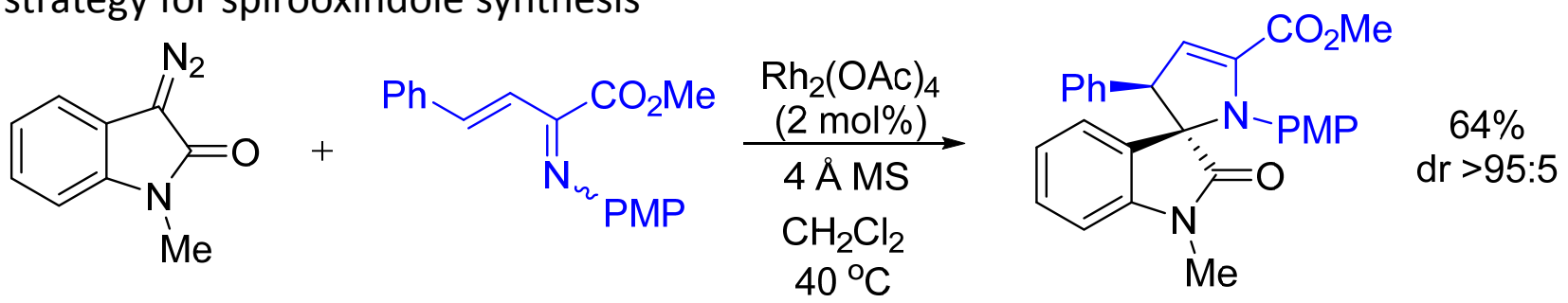
Failed Substrates:





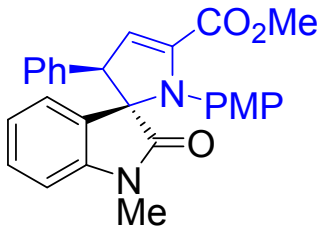


Our designed strategy for spirooxindole synthesis

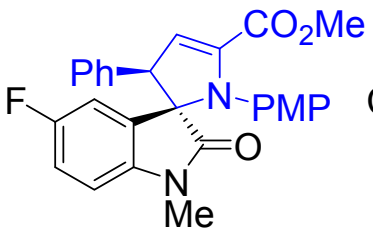


Entry	Cat. (mol%)	solvent	T (°C)	Yield (%)[b]	Dr[c]
1	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	40	64	> 95:5
2	$Rh_2(OAc)_4$ (2)	$CHCl_3$	40	51	> 95:5
3	$Rh_2(OAc)_4$ (2)	toluene	40	73	> 95:5
4	$Rh_2(OAc)_4$ (2)	EtOAc	40	60	> 95:5
5	$Rh_2(OAc)_4$ (2)	toluene	60	55	> 95:5
6	$Rh_2(OAc)_4$ (2)	toluene	15	77	> 95:5
7[d]	$Rh_2(OAc)_4$ (2)	toluene	15	68	> 95:5
8	$Cu(OTf)_2$ (10)	CH_2Cl_2	40	43	> 95:5
9	$CuPF_6(MeCN)_4$(10)	CH_2Cl_2	40	48	> 95:5

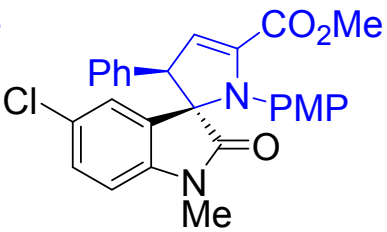
Unpublished Results



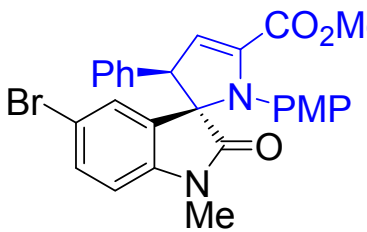
3a, 77%



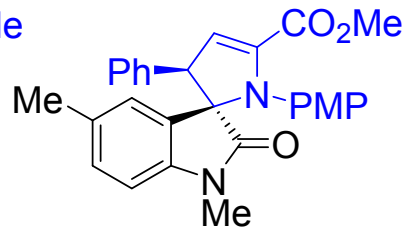
3b, 65%



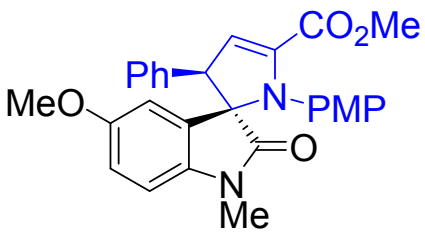
3c, 70%



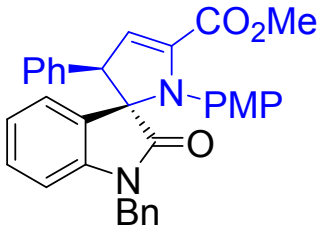
3d, 63%



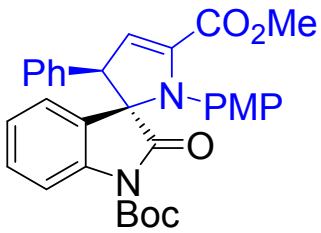
3e, 71%



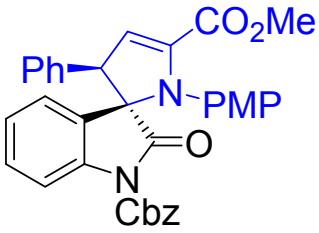
3f, 87%



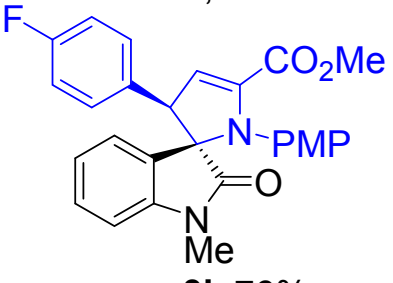
3g, 49%



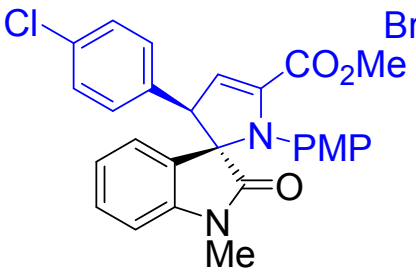
3h, 85%



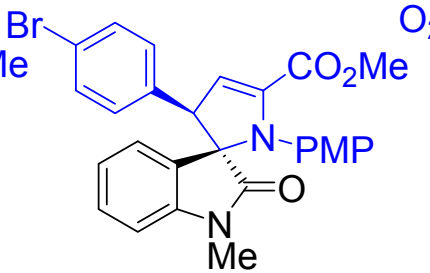
3i, 81%



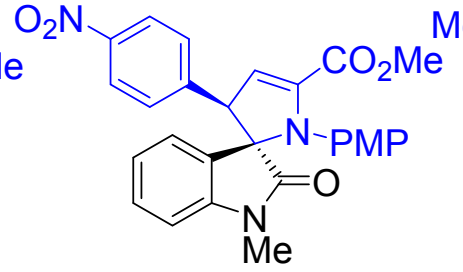
3j, 76%



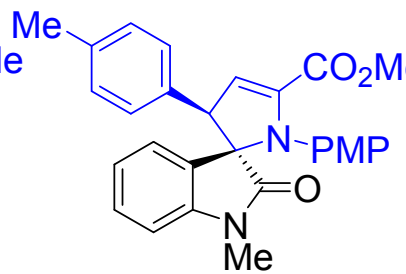
3k, 84%



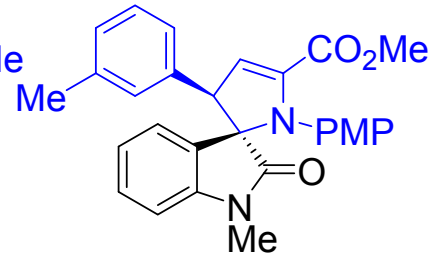
3l, 62%



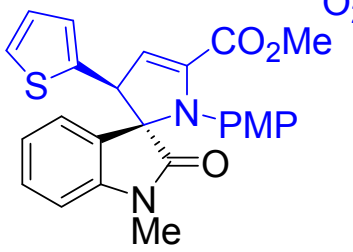
3m, 90%



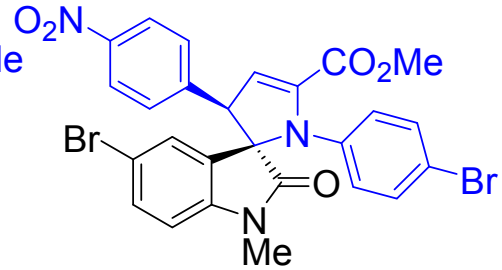
3n, 79%



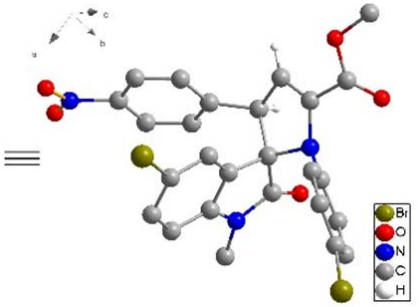
3o, 61%



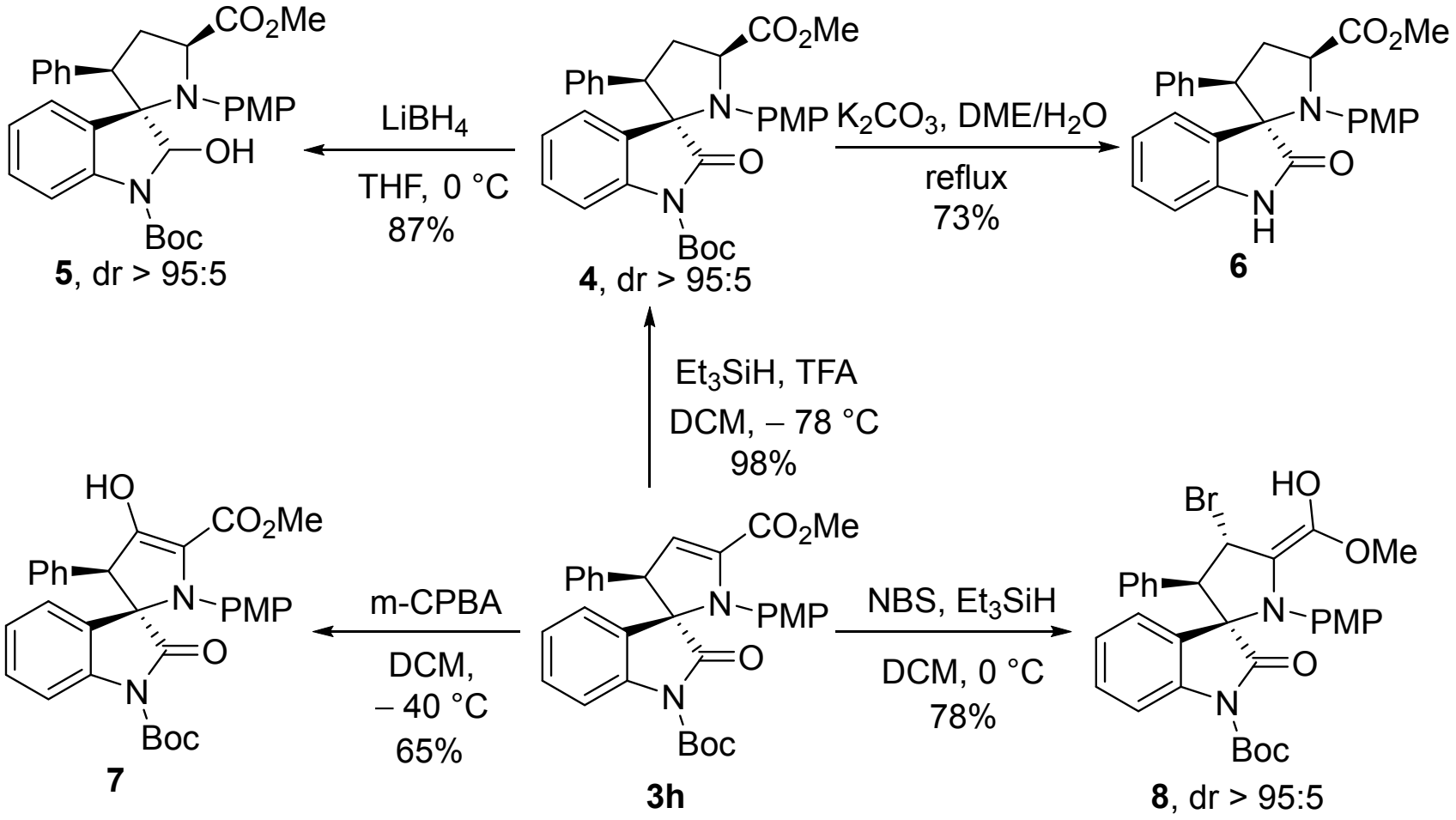
3p, 52%



3q, 96%

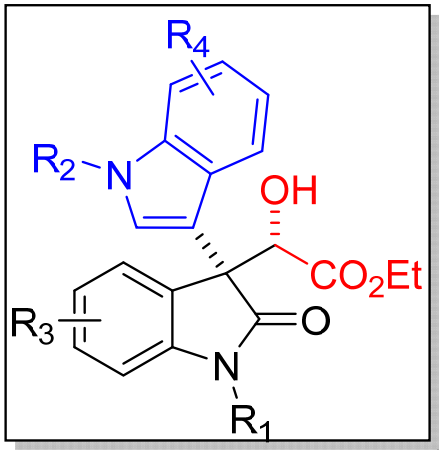


Unpublished Results

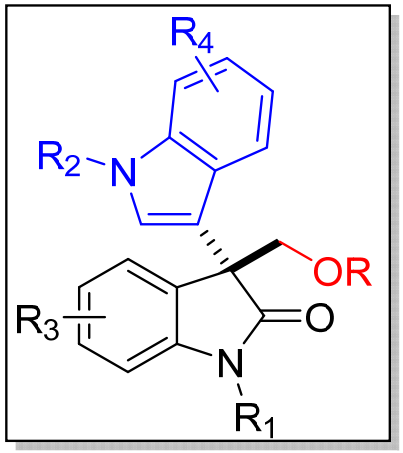


Unpublished Results

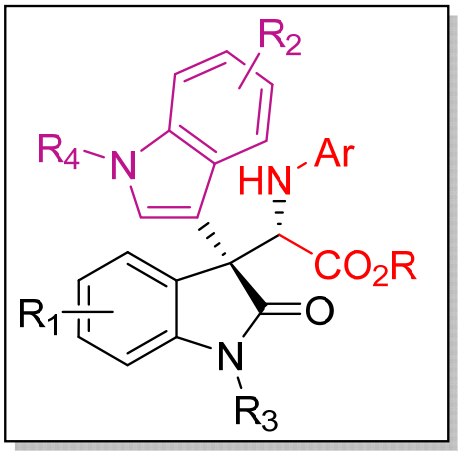
Initial Biological Evaluations



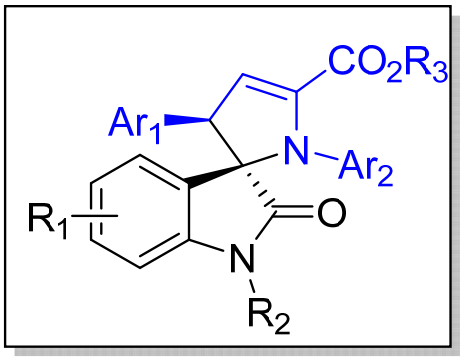
series 1
(23 cpds)



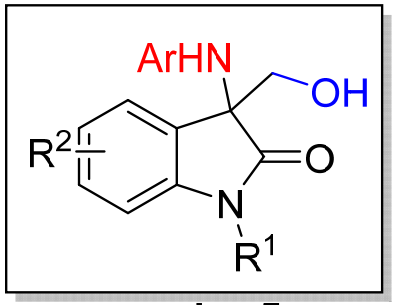
series 2
(14 cpds)



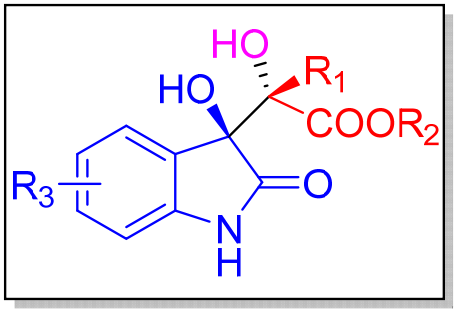
series 3
(20 cpds)



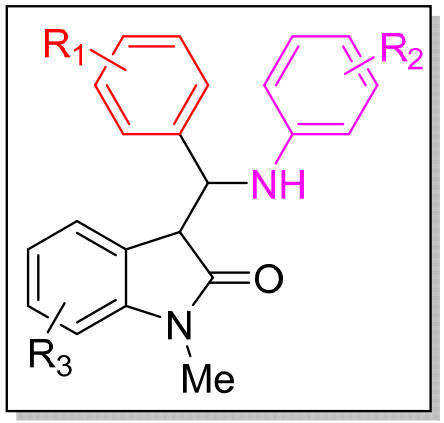
series 4
(19 cpds)



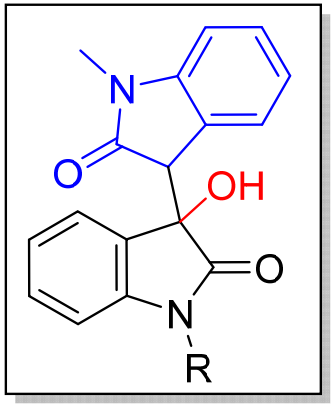
series 5
(21 cpds)



series 6
(20 cpds)

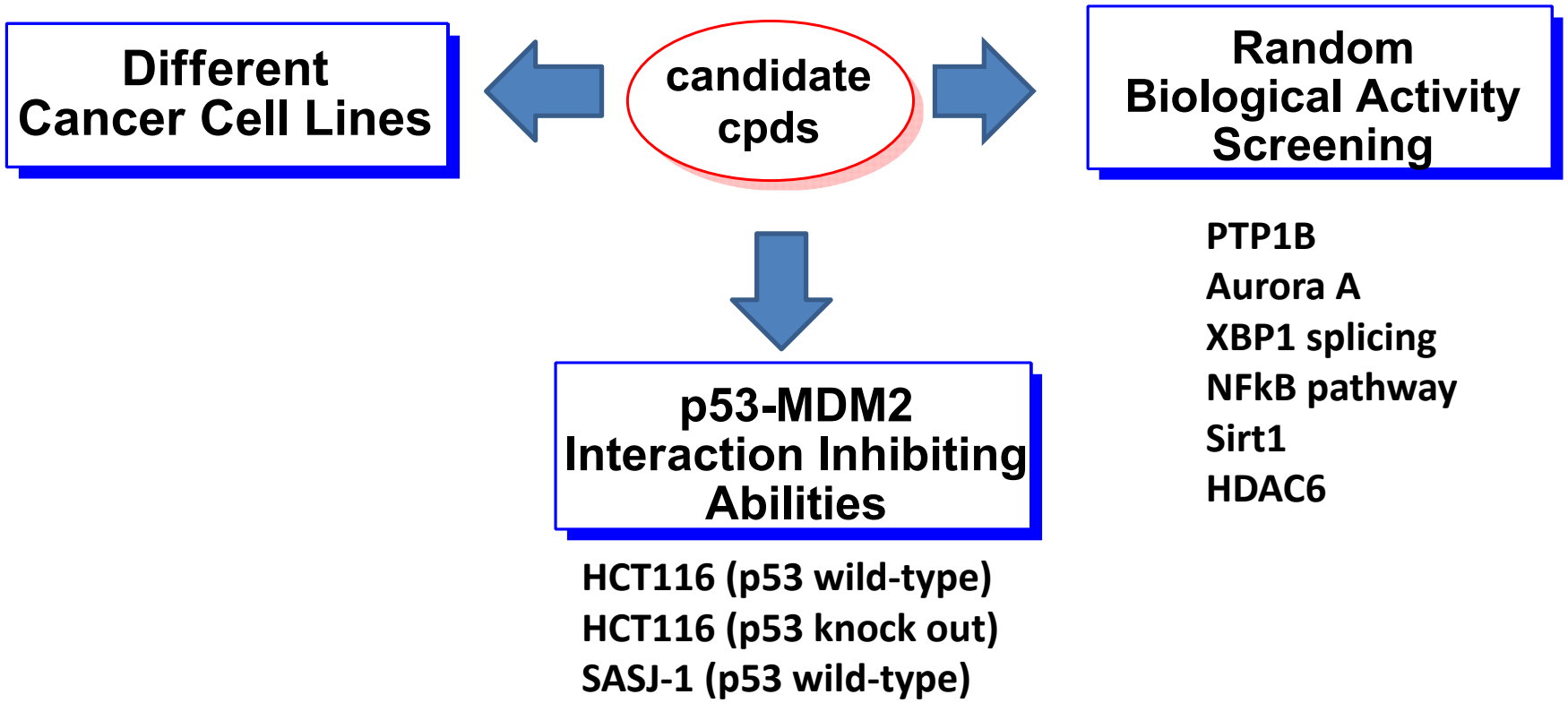


series 7
(23 cpds)



series 8
(19 cpds)

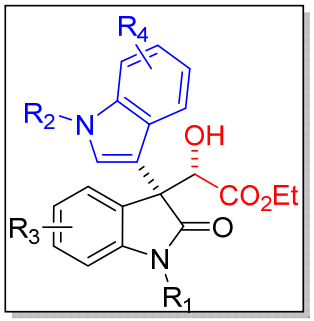
Initial Biological Evaluations



Collaborators: Prof. Jia Li's Group from National Center for Drug Screening of China

Initial p53-MDM2 interaction inhibiting

HCT116 (p53 wild-type & knock out)

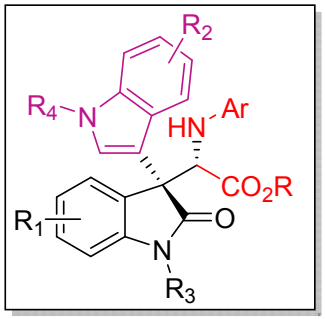


series 1
(23 cpds)

Entry	Cpd	IC_{50} (uM) HCT116 (wt)	IC_{50} (uM) HCT116 (ko)	Entry	Cpd	IC_{50} (uM) HCT116 (wt)	IC_{50} (uM) HCT116 (ko)
1	001	27.4	32.4	11	008	26.9	>100
2	018	8.9	21.1	12	009	5.7	21.8
3	002	19.9	14.1	13	021	37	29
4	004	26.8	31.5	14	007	17	25
5	003	19.9	21.3	15	017	23	50
6	006	35.4	10.9	16	012	85	19
7	010	17.7	21.4	17	013	15.5	>100
8	022	30.1	11.1	18	016	26	15
9	011	27.7	26.4	19	022	14.5	25.6
10	020	3.0	11.3	20	023	16	>100

Initial p53-MDM2 interaction inhibiting

HCT116 (p53 wild-type & knock out)



series 3
(19 cpds)

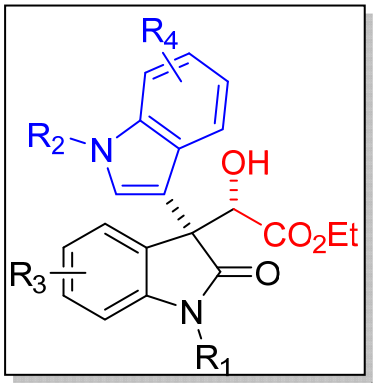
Entry	Cpd	IC_{50} (uM) HCT116 (wt)	IC_{50} (uM) HCT116 (ko)
1	301	16	> 100
2	302	25	200
3	303	23	60
4	304	27	67
5	305	26	24
6	306	12	30
7	307	21	34
8	308	14	25
9	309	17	25

Entry	Cpd	IC_{50} (uM) HCT116 (wt)	IC_{50} (uM) HCT116 (ko)
10	310	1.6	32
11	311	15	12
12	312	24	200
13	313	16	>100
14	314	20	>100
15	315	21	24
16	316	8.4	16.5
17	317	6.5	19
18	318	16	>100
19	319	12	>100

Antitumor activity-1

A549（Lung cancer cell line）

Entry	Cpd	IC_{50} (uM)	Entry	Cpd	IC_{50} (uM)
1	001	27.4	11	008	26.4
2	018	8.9	12	009	6.4
3	002	19.9	13	021	64.5
4	004	26.8	14	007	8.8
5	003	19.9	15	017	20.2
6	006	35.4	16	012	15.2
7	010	17.7	17	013	4.3
8	022	30.1	18	016	20.8
9	011	27.7	19	022	24.5
10	020	3.0	20	023	12.5



series 1
(23 cpds)

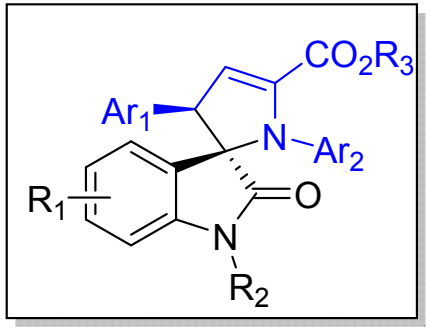
5 out of 23 cpds:
IC_{50} <10 μM

Antitumor activity-2

HCT116 (colon cancer cell line)

Entry	Cpd	IC_{50} (μM)
1	301	16
3	302	22
3	303	23
4	304	27
5	305	26
6	306	12
7	307	21
8	308	14
9	309	17

Entry	Cpd	IC_{50} (μM)
10	310	1.6
11	311	12
12	312	15
13	313	26
14	314	24
15	315	20
16	316	21
17	317	8.4
18	318	6.5
19	319	16

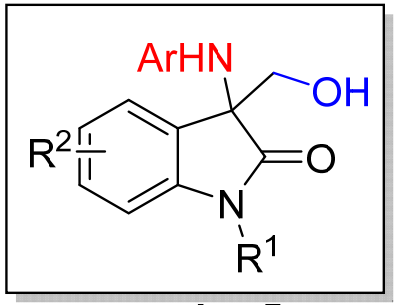


series 4
(19 cpds)

3 out of 19 cpds:
IC_{50} <10 μM

Antitumor activity-3

SASJ-1 (plasma cancer cell line)



series 5
(21 cpds)

Entry	Cpd	Inhibition @10 μM
1	WCJ001	44.09
2	WCJ002	29.64
3	WCJ003	12.09
4	WCJ004	24.34
5	WCJ005	9.34
6	WCJ006	19.75
7	WCJ007	92.65
8	WCJ008	62.01
9	WCJ009	87.74
10	WCJ010	52.60

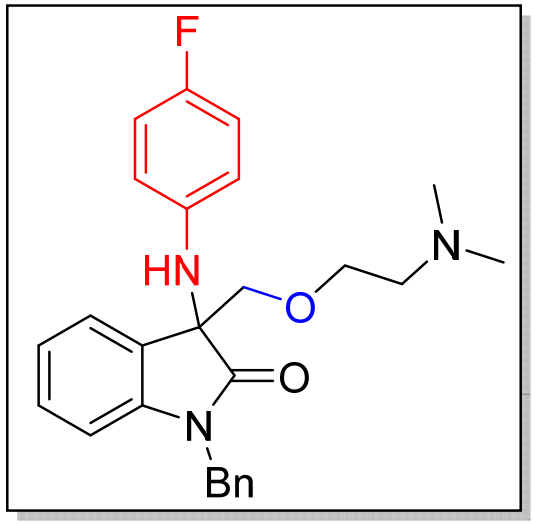
Entry	Cpd	Inhibition @10 μM
11	WCJ011	98.09
12	WCJ012	94.85
13	WCJ013	96.10
14	WCJ014	32.69
15	WCJ015	94.22
16	WCJ016	50.60
17	WCJ017	41.59
18	WCJ018	93.54
19	WCJ019	78.89
20	WCJ020	16.14
21	WCJ021	20.65

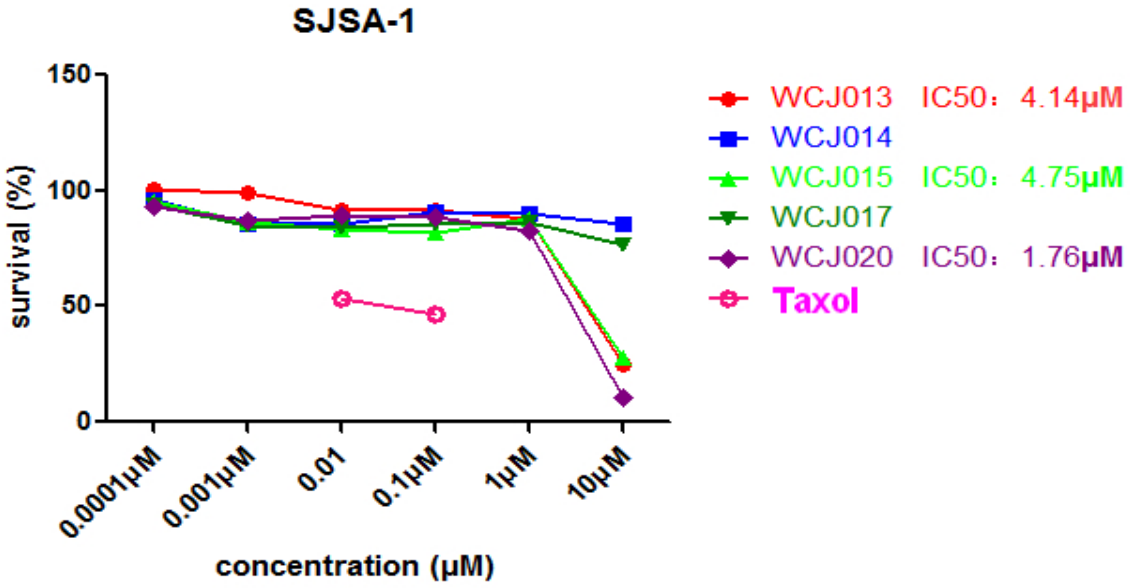
7 out of 21 cpds:
Inh% @10 μM > 85%

Antitumor activity-3

SASJ-1 (plasma cancer cell line)

Entry	Cpd	IC_{50} (μM)	Entry	Cpd	IC_{50} (μM)
1	WCJ007	>10	4	WCJ012	>10
2	WCJ009	>10	5	WCJ013	4.75
3	WCJ011	4.14	6	WCJ015	>10
			7	WCJ018	1.76





Thanks for Your Attention!